FDA

Antiviral Drugs Advisory Committee

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Briefing Document for Voriconazole

(Oral and Intravenous Formulations)

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Pfizer

EXECUTIVE SUMMARY

Fungal infections in immunosuppressed patients are associated with high morbidity and mortality, in particular those due to *Aspergillus spp.* (Patterson et al, 2000). The limited spectrum of antifungal activity, toxicity, and the lack of both an intravenous and an oral formulation for the same drug limit the likelihood of a successful patient outcome with available therapies. Voriconazole was developed to address this unmet medical need.

Voriconazole is a second generation triazole and is the result of a drug discovery program aimed at improving the potency and spectrum of fluconazole. Voriconazole was designed to retain the parenteral and oral formulation advantages of fluconazole while extending its spectrum to moulds, insufficiently treated yeasts, and less common fungal pathogens. The possibility of treatment using either intravenous or oral formulations allows flexibility in patient care and the possibility of prolonged treatment which is frequently required in invasive fungal infections.

Like other azole antifungals, voriconazole acts by inhibiting the cytochrome P450-dependent 14-α-sterol demethylase required for ergosterol biosynthesis, resulting in disruption of fungal membrane structure and function.

Voriconazole has broad *in vitro* antifungal activity against yeasts and moulds, including a wide range of less common pathogens. Voriconazole is fungicidal *in vitro* against all *Aspergillus spp.* and a range of moulds such as *Scedosporium spp.* and *Fusarium spp*., which have limited susceptibility to available antifungal agents. Voriconazole is also highly potent against *Candida spp* including *C. krusei*. This potent antifungal activity observed *in vitro* with voriconazole translates to excellent efficacy against *Aspergillus* and *Candida* in *in vivo* guinea pig models.

The clinical development program for voriconazole was designed to support the following treatment indications:

- Acute invasive aspergillosis
- Empirical treatment of presumed fungal infections in patients with persistent fever and neutropenia
- Other documented infections
  - Serious *Candida* infections
  - Infections due to emerging pathogens, including *Scedosporium spp.* or *Fusarium spp*.

This briefing document has been specifically prepared for the FDA Antiviral Advisory Committee Meeting to be held on October 4, 2001 which, at the request of the Division of Special Pathogen and Immunologic Drug Products, will primarily emphasize the data supporting voriconazole for the treatment of acute invasive aspergillosis and for the empirical treatment of patients with persistent fever and neutropenia. The clinical development program for voriconazole was extensive and much of the data is relevant to an understanding voriconazole's overall efficacy and safety profile as well as its clinical benefits and potential risks in these particular indications. Therefore the briefing document summarizes other important aspects of the voriconazole program including the pharmacokinetic, mycology and other clinical efficacy data.

Clinical Pharmacology and Dose Justification (Sections 6 & 9)

The pharmacokinetics of voriconazole are characterized by high oral bioavailability, a large volume of distribution, and elimination through hepatic metabolism by cytochrome P450 isozymes. The high oral bioavailability (96%) of voriconazole enables switching between intravenous and oral treatment. The large volume of distribution (4.6 L/kg) is consistent with extensive distribution into tissues. Voriconazole is extensively metabolized in the liver, with <2% excreted as unchanged drug. Saturable metabolism results in a more than proportional increase in exposure with increased oral and intravenous doses. Steady state plasma concentrations are achieved by Day 6 of dosing with 200 mg q 12 h but are approximated on Day 1 with a loading dose regimen (two doses of 6mg/kg IV or 400mg orally, 12 hours apart). Inter-individual variability in voriconazole pharmacokinetics is high and the factors involved in this variability have been extensively investigated. Higher exposure is seen in patients with chronic hepatic impairment or low body weight, in females and in the elderly. The clinical program has provided the appropriate pharmacokinetic information to facilitate dose selection, explain the pharmacokinetic variability and provide practical guidance on dosage adjustment in special populations where clinically relevant.

Studies with hepatic microsomes show voriconazole is metabolized by CYP2C19, CYP2C9 and CYP3A4, although its affinity for CYP3A4 is 100-fold lower than for CYP2C9 and CYP2C19. CYP2C19 exhibits genetic polymorphism. Potent inducers of these enzymes markedly decrease voriconazole plasma concentrations. Inhibitors of cytochrome P450 either have a minor or no effect on voriconazole exposure. Voriconazole, in turn, inhibits these enzymes, potentially increasing exposure to concomitant medications that are also metabolized by these pathways. The magnitude of interactions with CYP3A4 substrates is variable, ranging from no interaction (indinavir) to large increases in exposure (sirolimus). Results of a comprehensive array of *in vitro* and clinical pharmacology studies afford practical guidance on the management of drug interactions.

Doses of voriconazole were chosen for investigation on the basis of mycological, pharmacokinetic and clinical data. The intravenous dose regimen of 6mg/kg 12 hours apart for two doses, followed by maintenance doses of 3mg/kg q 12 h, rapidly achieved steady state plasma concentrations higher than the MICs for the majority of clinically relevant fungal pathogens. The Dose Ranging Oropharyngeal Candidiasis Study (302) provided preliminary evidence of efficacy and safety. The Multiple Dose Escalation IV/Oral Switch Study (230) established 4 mg/kg IV q 12 h or 300 mg orally q 12 h as the maximum tolerated dose. The dosing regimen used in clinical studies and recommended is: a maintenance dose of 3mg/kg IV q 12 h or 200mg orally q 12 h, with the option of dose escalation in the face of poor clinical response for infections due to *Candida* species and for empirical therapy. For the treatment of acute invasive aspergillosis and other mould infections, an intravenous maintenance dose regimen of 4 mg/kg q 12 h was chosen in recognition of the early and high mortality in these invasive fungal infections. In both cases, a loading dose regimen of two doses of 6 mg/kg IV or 400 mg orally 12 hours apart should be used.

The pharmacokinetic/pharmacodynamic analyses demonstrated statistically significant but weak relationships between plasma voriconazole concentration and the occurrence of liver function test abnormalities. No pharmacokinetic/pharmacodynamic relationship for efficacy was identified, probably due to confounding by other medical factors. However, data from the therapeutic studies confirmed that the dose regimens used achieved plasma voriconazole concentrations that exceed MICs for the majority of clinical isolates encountered. Post-filing analyses of the potential predictive value of plasma voriconazole concentration monitoring did not identify upper and lower threshold plasma concentrations that are predictive of liver function test abnormalities and therapeutic failure, respectively. Therefore, dosage individualization on the basis of plasma voriconazole concentration measurements is unlikely to add value over and above the monitoring of clinical response and liver function tests. In summary, analyses of the plasma voriconazole concentrations from therapeutic studies for pharmacokinetic/pharmacokinetic relationships, coverage of MICs and potential predictive performance confirm that the recommended dose regimens of voriconazole described below are appropriate for the proposed indications.

Several drugs are known to reduce the plasma concentration of voriconazole and therefore were not allowed as concomitant medication during the clinical development program (e.g., rifampin, carbamazepine, long-acting barbiturates). In addition, maintenance dosing was adjusted based on weight. Specific studies in hepatic impairment have clarified the extent of dose adjustment needed in this patient population. The recommended loading and maintenance doses are summarized below.

Voriconazole Dosage and Administration

	Intravenous	**Oral**	
		Patients ≥ 40kg	**Patients < 40kg**
Loading Dose Regimen (first 24 hours)	Two doses of 6mg/kg 12 hours apart	Two doses of 400mg 12 hours apart	Two doses of 200mg 12 hours apart
Maintenance Dose (after first 24 hours)*			
Serious *Candida* infections Empirical Therapy	3 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours
Invasive aspergillosis/ `*Scedosporium* and *Fusarium* infections/ Other serious mold infections	4 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours

* If patient response is inadequate, the maintenance dose of 3 mg/kg every 12 hours may be increased to 4 mg/kg every 12 hours for intravenous administration and to 300 mg every 12 hours for oral dosing. For patients less than 40 kg, the oral dose may be increased to 150 mg every 12 hours.

Monitoring of liver function tests is recommended. In patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) it is recommended that the standard loading dose regimens be used but that the maintenance dose be halved. Voriconazole has not been studied in patients with severe hepatic cirrhosis (Child-Pugh C). Voriconazole has been associated with elevations in liver function tests and should only be used in patients with severe hepatic insufficiency if the benefit outweighs the potential risk. Patients with hepatic insufficiency must be carefully monitored for drug toxicity.

Efficacy (Section 7)

The role of voriconazole in the treatment of fungal infections has been studied in an extensive clinical program that included: 4 large randomized controlled trials (305, 307/602, 603); one historical controlled study (304/1003); three uncontrolled studies in specific populations (303, 309, 604); and compassionate use studies that provided further evidence of safety and efficacy in the most difficult to treat patients. As of May 2001 over 2000 patients had been treated with voriconazole as part of this clinical development program. The majority of the patients enrolled in these studies were seriously ill and included patients with bone marrow transplants, graft *vs.* host disease, and prolonged neutropenia.

Aspergillosis (Section 7.1)

The data supporting the efficacy of voriconazole in the treatment of invasive aspergillosis depends on the results from both controlled and uncontrolled studies. The studies include: the randomized open label Global Comparative Aspergillosis Study (307/602), the Non-comparative Aspergillosis Study (304), the contemporaneous Historical Controlled Study (1003); and a pooled analysis of patients from all other uncontrolled studies with documented baseline aspergillosis prior to initiation of voriconazole treatment.

The Global Comparative Aspergillosis Study (307/602), the large randomized comparative study conducted to investigate the initial treatment of this patient population, enrolled a total of 392 patients with documented invasive aspergillosis at sites in the United States, Europe, Israel, Canada, Australia, Brazil, Argentina, Colombia, Mexico, and India. The study met the protocol-specified criteria for efficacy and a higher proportion of voriconazole-treated patients had a successful outcome as assessed by a blinded Data Review Committee at Week 12, compared with the current standard therapy for invasive aspergillosis (amphotericin B, which was followed in this study by Other Licensed Antifungal Therapy). The treatment effect was also seen at the end of randomized therapy. Kaplan-Meier plots show an early and continued survival benefit in favor of voriconazole.

Eligible patients were randomized to receive up to 12 weeks of treatment with either voriconazole IV/oral or intravenous amphotericin B followed by other licensed antifungal therapy. Voriconazole was administered with 2 loading doses of 6 mg/kg IV q 12 h followed by 4 mg/kg q 12 h for a least 7 days followed by oral voriconazole 200 mg bid up to a total of 12 weeks. Amphotericin B was administered at a dose of 1.0-1.5 mg/kg/day as a slow IV infusion for 14 days. In both treatment groups, patients were allowed to switch to other licensed antifungal therapies if they failed to respond or were unable to tolerate the initial randomized therapy.

A Modified Intention-to-Treat population was defined based on administration of a least one dose of randomized treatment and a definite or probable diagnosis of aspergillosis at baseline as determined by an independent blinded Data Review Committee. The Modified Intention to Treat population included 144 patients in the voriconazole group and 133 patients in the amphotericin B group. Patients receiving voriconazole were more likely to remain on randomized treatment: the median duration of treatment was 77 days, with 43% of patients completing the treatment period on randomized treatment, compared with an 11 day median treatment duration for amphotericin B and 1.5% of patients remaining on randomized treatment to Week 12.

The primary end point was success (complete or partial response) at Week 12 as assessed by the Data Review Committee. As shown below for both studies individually and combined, there were consistently more successful outcomes in the voriconazole arm.

Global Comparative Aspergillosis Study (307/602) - MITT Population
Data Review Committee-Assessed Outcome at Week 12 by Study

Outcome*	Voriconazole			Amphotericin B		
	Study 602 (N=58) n (%)	Study 307 (N=86) n (%)	Total (N=144) n (%)	Study 602 (N=49) n (%)	Study 307 (N=84) n (%)	Total (N=133) n (%)
Success	27 (46.6)	49 (57.0)	76 (52.8)	11 (22.5)	31 (36.9)	42 (31.6)
Failure	31 (53.5)	37 (43.0)	68 (47.2)	38 (77.6)	53 (63.1)	91 (68.4)

*Success = cure or improvement; failure = stable, failure, indeterminate, or missing response

The adjusted (by protocol) analysis of success is shown below. Because the lower limit of the approximate two-sided 95% confidence interval for the difference in success rates (voriconazole arm minus amphotericin B arm) did not fall below –20%, the response to treatment in the voriconazole arm was considered to be non-inferior to the response in the amphotericin B arm. Moreover, since the confidence interval excludes 0, the voriconazole regimen is considered statistically superior to the amphotericin B regimen.

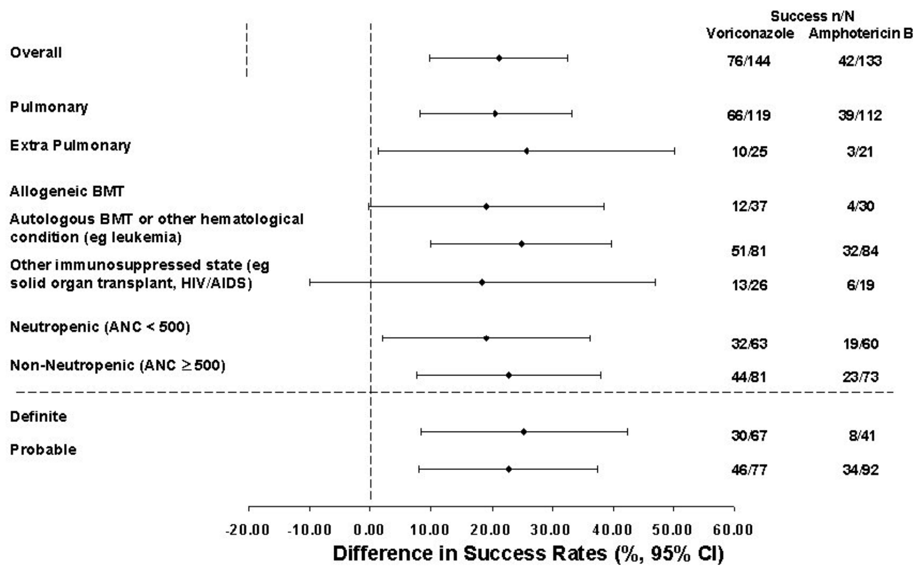
Global Comparative Aspergillosis Study (307/602) - MITT Population
Data Review Committee-Assessed Outcome at Week 12

Outcome	Voriconazole (N=144)	Amphotericin B (N=133)	Difference Voriconazole - Amphotericin B	*p* value
Proportion of patients with success (adjusted for protocol)	52.8%	30.6%	21.8%	<0.0001
95% CIs	44.70, 60.93	22.84, 38.30	10.54, 32.97	-

Success = cure or improvement; CI = confidence interval

The following figure demonstrates that the outcome for the overall primary analysis population was consistently observed irrespective of site of infection, underlying disease, neutrophil state, or certainty of infection.

Global Comparative Aspergillosis Study (307/602) Analysis - MITT Population
Data Review Committee-Assessed Outcome at Week 12 Subgroup Analysis



A secondary endpoint was survival through Day 84 post-randomization. By Day 84, 102 patients initially treated with voriconazole were still alive, compared with 77 amphotericin B patients. The difference in survival between the two treatment arms showed a hazard ratio (adjusted for protocol only) of 0.6 (95% confidence interval: 0.4, 0.9). As shown below, the blinded Data Review Committee-assessed cause of death, the mortality difference between treatment arms was primarily due to death caused by aspergillosis.

Global Comparative Aspergillosis Study (307/602) - MITT Population
Data Review Committee-Assessed Cause of Death at Day 84

Cause of Death	Voriconazole/OLAT (N=144)	Amphotericin B/OLAT (N=133)
Alive at Day 84	102 (70.8)	77 (57.9)
Dead at Day 84	42 (29.2)	56 (42.1)
Death caused by aspergillosis	18 (12.5)	38 (28.6)
Death unrelated to aspergillosis but evidence of residual aspergillosis present	10 (6.9)	8 (6.0)
Death unrelated to aspergillosis and no evidence of residual aspergillosis	7 (4.9)	3 (2.3)
Indeterminate	7 (4.9)	4 (3.0)
Not assessed by Data Review Committee*	0	3 (2.3)

OLAT = Other Licensed Antifungal Therapy
*These 3 patients were not assessed because they died after withdrawal from the study.

The success rates seen with voriconazole in the randomized open label Global Comparative Aspergillosis Study (307/602) confirmed the results of the earlier Non-Comparative Aspergillosis Study (304) for which a matched cohort of patients were retrospectively identified as a contemporaneous historical control (1003). Similar to patients in the Non-

Comparative Aspergillosis Study (304), the patients in the historical control group were entered into the study based on the number of days of prior antifungal therapy, as well as documentation of invasive aspergillosis. The results of the matched comparison based on an assessment of outcome are shown below.

A survival analysis at 90 days in that cohort of patients with <5 days of previous antifungal treatment showed a separation similar to that seen in the randomized open label Global Comparative Aspergillosis Study.

Non-Comparative Aspergillosis Study (304) *vs.* Historical Control Study (1003)
Patients with <5 days prior therapy*

	Voriconazole Study 304 (N=50) n (%)	**Historical Control Study 1003 (N=92) n (%)**
Clinical Outcome		
Success (complete or partial)	26 (52.0)	23 (25.0)
Survival at 90 Days		
Alive	26 (52.0)	32 (34.8)
Dead	22 (44.0)	52 (56.5)
Censored	2 (4.0)	8 (8.7)
Probability of survival Approximate 95% confidence interval	0.55 (0.42, 0.69)	0.42 (0.31, 0.52)

*Duration of prior therapy as assessed by Sponsor.

Together, the pivotal randomized open label Global Comparative Aspergillosis Study (307/602) and supportive Non-Comparative Aspergillosis Study (304) document the efficacy of voriconazole in the treatment of acute invasive aspergillosis, demonstrating a more favorable outcome compared to standard antifungal therapy. In particular, the poor outcome observed in the Historical Control Study (1003), conducted approximately five years earlier, was again seen in the comparator arm of the Global Comparative Aspergillosis Study (307/602). In these studies, voriconazole showed an approximately 22 % higher success rate than amphotericin B.

Empirical Therapy (Section 7.2)

Invasive fungal infections are increasingly adding to morbidity and mortality in immunocompromised patients, especially those undergoing chemotherapy or bone marrow transplantation for cancer. Although empirical antifungal therapy has been shown to reduce the emergence of breakthrough fungal infections, available treatment options are limited by deficiencies in spectrum, pharmacokinetic profile or toxicity.

The Empirical Therapy Study (603/MSG42) was a randomized open-label study that compared voriconazole to liposomal amphotericin B as empirical antifungal therapy in immunocompromised patients with persistent fever and neutropenia. Dose and duration of therapy were flexible, dependent on the underlying condition and response of the patient. Following randomization, during the period of neutropenia and the treatment period after recovery from neutropenia, the investigator evaluated the patient daily for the presence of bacterial or fungal infection, body temperature, and absolute neutrophil count, according to protocol specifications.

Randomization was stratified according to risk of developing invasive fungal infection (high risk: allogeneic transplant or relapsed leukemia; moderate risk: autologous transplant, newly diagnosed leukemia or other neoplasm) as well as previous use of systemic antifungal prophylaxis. Patients were treated with study drug up to three days after recovery from neutropenia or for up to 12 weeks in the event of confirmed baseline or breakthrough fungal infection. Success was based on a composite endpoint requiring all five of the following:

- Survival through seven days following end of therapy
- No breakthrough fungal infections during neutropenia or within seven days after discontinuation of study medication
- Defervescence prior to recovery from neutropenia
- No discontinuation of study treatment due to toxicity or lack of efficacy prior to recovery from neutropenia
- Complete or partial global response at end of therapy (for patients with baseline infections).

The protocol-defined primary analysis was a comparison between treatment groups (MITT population) based on a stratified (adjusted for risk of infection, previous systemic prophylaxis, and duration of baseline neutropenia) 95% confidence interval for the difference in the success rates, with non-inferiority based on a margin of –10%.

A Data Review Committee, blinded with regard to treatment assignment, evaluated any patient with a potential diagnosis of deeply invasive fungal infections for the presence of infection, type of infection (baseline or breakthrough), certainty of infection (definite or probable), and global response at the End of Therapy.

Based on the composite endpoint, a successful outcome was achieved in 23.7% of patients treated with voriconazole compared with 30.1% of patients treated with liposomal amphotericin B. The stratified difference between groups was –6.1% with the approximate two-sided 95% confidence intervals around the difference [–12.0 to –0.1]. Since the lower limit of the confidence interval was below –10%, voriconazole did not demonstrate non-inferiority to liposomal amphotericin B.

The following table summarizes overall raw (unadjusted) response to empirical therapy together with the response for each of the five components of the endpoint.

Empirical Therapy Study (603/MSG42) - MITT Population
Overall Response and Response by Component

Response Parameters	Voriconazole (N=415) n (%)	L-AMB (N=422) n (%)	Difference(Raw): Voriconazole - L-AMB 95% CI
Overall response to empirical therapy	108 (26.0)	129 (30.6)	-4.5 (-10.6, 1.6)
No breakthrough fungal infections within 7 days of End of Therapy	407 (98)	401 (95)	3.1 (0.6, 5.5)
Survival through 7 days of End of Therapy	382 (92)	397 (94)	-2.0 (-5.5, 1.4)
No discontinuation due to toxicity or lack of efficacy before recovery from neutropenia	374 (90)	394 (93)	-3.2 (-7.0, 0.5)
Resolution of fever during neutropenia	135 (33)	154 (36)	-4.0 (-10.4, 2.5)
Global response of baseline fungal infections at End of Therapy (Complete or partial response)	6/13 (46)	4/6 (67)	-20.5 (-67.0, 25.9)

L-AMB = Liposomal amphotericin B

The lower than expected overall success in both treatment arms was due to the failure of many patients to defervesce before recovery from neutropenia.

There were fewer cases of breakthrough invasive fungal infections in voriconazole compared with liposomal amphotericin B treated patients (8 versus 21, respectively). Four cases of aspergillosis, all pulmonary, occurred in voriconazole treated patients in comparison to 13 cases in liposomal amphotericin B treated patients. Disseminated, sinus, and central nervous system aspergillosis occurred only in liposomal amphotericin B treated patients. There were two cases of invasive candidiasis in the voriconazole arm in comparison to six in the liposomal amphotericin B arm. Zygomycosis (n = 2) occurred only in the voriconazole treated patients, while dematiaceous mould infections (n = 2) occurred only in liposomal amphotericin B treated patients.

In this study the randomization was stratified by risk of developing invasive fungal infections, *i.e.* high risk patients (those with allogeneic bone marrow transplants and relapsed leukemia) and moderate risk patients (those with autologous transplants, newly diagnosed leukemia and other neoplasms). Overall outcomes and components of the composite endpoint for the high risk and moderate risk patients are summarized below.

Empirical Therapy Study (603/MSG42) – MITT Population
Overall Response and Response by Component – High Risk and Moderate Risk Patients

Response Parameters	High Risk			Moderate Risk		
	Voric. N=143 %	L-AMB N=141 %	Point est. (Raw) 95% CI	Voric. N=272 %	L-AMB N=281 %	Point est. (Raw) 95% CI
Overall response to empirical therapy	31.5	29.8	1.7 (-9.0, 12.4)	23.2	31.0	-7.8 (-15.2, 0.4)
No breakthrough fungal infections within 7 days of End of Therapy	98.6	90.8	7.8 (2.7, 13.0)	97.8	97.2	0.6 (-2.0, 3.3)
Survival through 7 days of End of Therapy	91.6	90.8	0.8 (-5.8, 7.4)	92.3	95.8	-3.5 (-7.4, 0.5)
No discontinuation due to toxicity or lack of efficacy before recovery from neutropenia	92.3	92.2	0.1 (-6.1, 6.3)	89.0	94.0	-5.0 (-9.6, -0.3)
Resolution of fever during neutropenia	38.5	(39.0	-0.6 (-11.9, 10.8)	29.4	35.2	-5.8 (-13.6, 2.0)
Global response of baseline fungal infections at End of Therapy (Complete or partial response)	2/5	3/4	-95.4 (-95.4, 25.4)	4/8	1/2	0 (-77.5, 77.5)

est. = estimate; L-AMB = liposomal amphotericin B; Voric. = voriconazole

The following table presents the frequency of breakthrough infections separately for high and moderate risk patients.

Empirical Therapy Study (603/MSG42) - MITT Population
Breakthrough Infections by Risk

	Voriconazole	Liposomal Amphotericin B
High Risk	2/143 (1.4)	13/141 (9.2)
Moderate Risk	6/272 (2.2)	8/281 (2.8)
ALL	8/415 (1.9)	21/422 (5.0)

The effect of voriconazole in prevention of breakthrough fungal infections was more pronounced in the patients prospectively defined as being at high risk of developing fungal infections (2 voriconazole-treated patients *vs.* 13 liposomal amphotericin B-treated patients).

In the Empirical Therapy Study (603), voriconazole did not fulfill the statistical criteria to show non-inferiority to liposomal amphotericin B as assessed by the composite endpoint. Voriconazole therapy was associated with fewer documented breakthrough invasive fungal infections than was therapy with liposomal amphotericin B. The results of the Empirical Therapy Study (603), supported by the results of the efficacy in patients with documented fungal infections demonstrate that voriconazole may be considered an appropriate alternative to liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia.

Candidiasis

The Esophageal Candidiasis Study (305, Section 7.3), a large randomized double-blind study, showed voriconazole to be not inferior to fluconazole in successfully treating endoscopically- and mycologically-proven cases of esophageal candidiasis. Overall, voriconazole produced endoscopically-proven success in 98.3% of the per protocol population. This study included a subset of patients with advanced AIDS, defined as CD4 cell count ≤50 cells/mm^3, as well as a subset with Grade III-IV esophagitis. The results of this study provided evidence of efficacy in *Candida* infections prior to pursuing the study of voriconazole in the treatment of more invasive *Candida* infections. The Global Comparative Candidemia protocol (608) is an evaluation of voriconazole compared to conventional amphotericin B followed by fluconazole in the treatment of candidemia in non-neutropenic patients. This study protocol was submitted in Feb. 1998 and is ongoing, with over half of the targeted patients (426) enrolled to date.

Pooled Analyses: Aspergillosis, Systemic Candidiasis, Emerging Pathogens (Appendix 4)

Pooled analyses were conducted across a variety of controlled, uncontrolled and compassionate use studies in order to allow consistent assessment of patients with respect to certainty of diagnosis and outcome following voriconazole treatment. Patients were included only if they had a definite or probable infection and adequate information for evaluation.

In the analysis for aspergillosis (which did not include the Global Comparative Aspergillosis Study [307/602]), 332 patients were identified with a diagnosis of definite or probable *Aspergillus* infection. A success rate of 40.3% was observed in the 248 patients who had received voriconazole as salvage therapy (>5 days of prior systemic antifungal therapy), including patients with central nervous system involvement.

In the analysis for candidiasis, summary efficacy information was identified for 91 patients with documented serious systemic *Candida* infection. This includes 43 patients who received voriconazole as salvage therapy, 36 of whom were classified as previous efficacy failures after treatment with one or more previous antifungal agents. Success was seen in 22 of 43 patients (51.2%).

There were 35 patients with documented *Scedosporium* infections in the pooled analysis. Successful outcomes were observed in 16 of 27 patients (59.3%), with infections due to *S. apiospermum* and 2 of 8 patients with infections due to *S. prolificans*. Six of 15 patients with *Fusarium* infections in the pooled analysis had successful outcomes.

Safety (Section 8)

The overall pooled safety database, including extension and compassionate use studies consists of a total of 2090 patients with severe underlying immunosuppressive conditions. Of these, 1493 patients were involved in the therapeutic trials. An additional 1150 patients and healthy volunteers participated in clinical pharmacology studies, including drug interaction studies, assessments of visual effects, effect of hepatic impairment, effect of renal impairment, effect in pediatric patients and assessment of pharmacogenetic variation.

Of the 1493 patients who received voriconazole in a therapeutic study, 21.3% received greater than 12 weeks of treatment. In the overall pooled patient population (N=2090) 136 patients (6%) received more than 6 months of treatment. The most frequent adverse events, regardless of causality assessment, leading to discontinuation from voriconazole in the overall pooled patient population were elevated alkaline phosphatase (1.4%), acute kidney failure (1.3%), abnormal liver function tests (1.1%), increased hepatic enzymes (1.0%), sepsis (1.0%) and rash (1.0%).

The serious condition of the patients requiring treatment with voriconazole is underscored by the 40% mortality in the overall patient population. However, a survival benefit was seen for voriconazole treated patients compared to amphotericin B-treated patients in the combined analysis of the Global Comparative Aspergillosis Study (307/602) at 84 days after randomization and this was sustained at 30 days after therapy terminations.

The most frequently reported all-causality serious adverse event in the overall voriconazole treated population (N=2090) was sepsis (11.7%), while the most frequent serious adverse event judged to be potentially treatment-related was acute renal failure (1.1%). The most frequent non-serious adverse events reported in the therapeutic and overall pooled patient populations are shown in the table below.

Pooled Safety Database
Most Frequently Reported All Causality Treatment Emergent Adverse Events

Adverse Events*	**Voriconazole Therapeutic Studies (N = 1493) n (%)**	**Voriconazole Overall Pooled (N = 2090) n (%)**
Abnormal vision	358 (24.0)	422 (20.2)
Fever	324 (21.7)	430 (20.6)
Rash	268 (18.0)	362 (17.3)
Vomiting	259 (17.3)	327 (15.6)
Nausea	229 (15.3)	269 (12.9)
Diarrhea	215 (14.4)	282 (13.5)
Headache	191 (12.8)	233 (11.1)
Sepsis	175 (11.7)	259 (12.4)
Peripheral Edema	176 (11.8)	211 (10.1)
Respiratory Disorder	159 (10.6)	229 (11.0)

*Reported in ≥10% of voriconazole patients in either population

Assessment of all the available information suggest that the risks associated with voriconazole use include abnormal vision, hepatic function abnormalities, skin reactions and the potential for drug interactions. Each of these adverse event categories occurred more frequently in voriconazole-treated patients than in patients treated with comparators. These adverse events were examined in more detail either through additional studies or additional analysis of the existing clinical and nonclinical data or some combination of these approaches.

Although abnormal vision was reported as an adverse event by 24% of patients in Therapeutic Studies and approximately 35% of healthy volunteers, it resulted in treatment discontinuation in only 8/1493 (0.5%) patients in Therapeutic Studies and 3/443 (0.7%) healthy volunteers. The majority occurred early in treatment. Reports of visual disturbances on voriconazole can be classified into four categories: altered/enhanced visual perception, blurred vision, color vision change and photophobia. Mechanistic studies showed the site of voriconazole effect in both humans and dogs to be within the retina. The results of these studies confirmed that the effect of voriconazole on visual function is transient and reversible and without long-term sequelae in animals and humans.

Hepatic function abnormalities tend to be reported at high rates in clinical trials of all antifungal agents. In the controlled clinical trials of voriconazole compared to either conventional amphotericin B (Study 307/602) or liposomal amphotericin B (Study 603), the frequency of abnormal liver function tests was not substantially different between the treatment groups based on baseline liver function. The data from the largest and longest controlled clinical trial of voriconazole (Study 307/602) is shown below.

Global Comparative Aspergillosis Study (307/602) - Safety Population
Occurrence of Clinically Significant Hepatic Function Test Abnormalities

Clinically Significant Hepatic Function Test Abnormalities	Hepatic Laboratory Parameter	Voriconazole (N = 196) n (%)	Amphotericin B/OLAT (N = 185) n (%)
Without regard to baseline*	Total bilirubin	35/180 (19.4)	46/173 (26.6)
	AST	21/180 (11.7)	18/174 (10.3)
	ALT	34/180 (18.9)	40/173 (23.1)
	Alkaline Phosphatase	29/181 (16.0)	38/173 (22.0)
With normal baseline*	Total bilirubin	13/135 (9.6)	29/148 (19.6)
	AST	15/147 (10.2)	9/136 (6.6)
	ALT	18/120 (15.0)	20/115 (17.4)
	Alkaline Phosphatase	8/114 (7.0)	17/118 (14.4)
With abnormal baseline**	Total bilirubin	7/45 (15.6)	11/25 (44.0)
	AST	4/33 (12.1)	8/38 (21.1)
	ALT	11/60 (18.3)	13/58 (22.4)
	Alkaline Phosphatase	17/67 (25.4)	19/55 (34.5)

ALT = alanine transaminase; AST = aspartate transaminase; OLAT = Other Licensed Antifungal Therapy
*Clinically significant defined as: total bilirubin mg/dL > 1.5 x ULN; AST, ALT, alkaline phosphatase IU/ L > 3 x ULN
**Clinically significant defined as: total bilirubin, AST, ALT, alkaline phosphatase > 1.5 x baseline

In the overall voriconazole development program, there were 26 patients with a report of hepatic failure leading to death; 19/2090 (0.9%) on voriconazole and 7/856 (0.8%) on active comparator (all were receiving amphotericin B formulations). After the New Drug Application was filed, an independent expert panel of hepatologists performed a blinded review of all cases of hepatic failure leading to death. The panel determined that one case could be potentially related to voriconazole treatment. Data suggest that hepatic function test abnormalities occurring with voriconazole are reversible following dose reductions or withdrawal of the drug.

Skin reactions were observed in 17.3% (362/2090) of voriconazole-treated patients. Most skin reactions were not severe and did not require discontinuation of treatment.

Frequency of Rash Reported as an Adverse Event and Discontinuations due to Rash in Various Populations

Population Treatment Group	Incidence of rash	
	Total n/N (%)	Leading to discontinuation n/N (%)
Therapeutic Studies - Voriconazole	278/1493 (18.6%)	13/1493 (0.9%)
Overall Pooled -- Voriconazole	362/2090 (17.3%)	17/2090 (0.8%)
Esophageal Candidiasis Study (305)		
Voriconazole	11/200 (5.5%)	2/200 (1.0%)
Fluconazole	10/191 (5.2%)	0
Empirical Treatment Study (603)		
Voriconazole	96/421 (22.8%)	2/421 (0.5%)
Liposomal amphotericin B	105/428 (24.5%)	3/428 (0.7%)
Comparative Aspergillosis Study (307/602)		
Voriconazole	45/196 (23.0%)	2/196 (1.0%)
Amphotericin B/Other Licensed Antifungal Therapy	21/185 (11.4%)	1/185 (0.5%)

Two patients were reported with Stevens-Johnson syndrome, one patient was reported with erythema multiforme and one patient had an event described as toxic epidermal necrolysis. Of these, the cases of erythema multiforme and toxic epidermal necrolysis were considered serious and a relationship to voriconazole could not be ruled out. In the overall pooled safety population, 41 (2.0%) of 2090 patients receiving voriconazole reported events that coded to the preferred term of photosensitivity reaction. Two of these 41 patients were discontinued as a result of photosensitivity. Neither voriconazole nor its principal metabolite, UK-121,265, has significant absorption in the region of the UV A spectrum usually associated with photosensitivity (320-400 nm).

In summary, the safety profile of voriconazole is acceptable for the severely ill patient population where it is likely to have the most use. In addition, the safety profile is superior to that of amphotericin B formulations. Overall assessment indicates that the safety profile of voriconazole is characterized by hepatic function abnormalities, visual disturbances and skin reactions. For other adverse events, the relationship to voriconazole treatment is less clear. The visual events are transient, reversible and without long-term sequelae. The risk of hepatic function abnormalities can be managed by monitoring hepatic function tests. Skin reactions rarely disrupt therapy with voriconazole.

Conclusions

Fungal infections occur in severely ill, immunocompromised patients and are associated with high morbidity and mortality. Currently available therapeutic options are limited by poor spectrum of antifungal activity, toxicity, and the lack of both intravenous and oral formulations. Voriconazole addresses this unmet medical need. It has been shown to be efficacious in the treatment of fungal infections due to *Aspergillus* spp., demonstrating improvement in clinical outcomes and survival. Clinical outcomes were improved in patients with infections due to emerging pathogens, including those caused by *Scedosporium* spp. and *Fusarium* spp., and in patients with central nervous system infections. Voriconazole was shown to be not inferior to fluconazole in the treatment of endoscopically and mycologically proven esophageal candidiasis and patients with serious system Candida infections had reassuring efficacy results. In a large trial evaluating the efficacy of voriconazole in the empirical treatment of patients with persistent fever and neutropenia, voriconazole did not fulfill the statistical criteria for demonstration of non-inferiority in the composite endpoint, but was associated with fewer breakthrough fungal infections than the comparator, liposomal amphotericin B. This effect was more pronounced in patients with allogeneic bone marrow transplants or relapsed leukemia.

Safety assessment in over 2000 patients demonstrates that voriconazole is associated with visual abnormalities, hepatic function abnormalities, skin reactions, and, because of its metabolic pathway involving cytochrome P450 isozymes, the potential for drug interactions. Visual abnormalities are transient and reversible. An extensive nonclinical and clinical evaluation suggests that the retina is the target site but there is no evidence to suggest long term sequelae. Liver function test monitoring during voriconazole treatment is recommended. Voriconazole may be associated with photosensitivity skin reactions; patients who experience photosensitivity should avoid sunlight. Specific guidance for management of potential drug interactions has been developed as a result of a large, comprehensive clinical pharmacology program.

Voriconazole was demonstrated to be better tolerated than amphotericin B formulations. Patients were maintained on therapy for longer durations and voriconazole was associated with fewer infusion related reactions, less hypokalemia, and fewer increases in serum creatinine. In a comparison with fluconazole in a primarily HIV positive population of patients with esophageal candidiasis, the safety profile of voriconazole was acceptable; however, more patients discontinued therapy with voriconazole and there were more liver function test abnormalities with voriconazole.

In summary, voriconazole has established a favorable risk: benefit profile in the treatment of serious fungal infections.

TABLES

FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AEM	Adverse event monitoring
AIDS	Acquired Immunodeficiency Syndrome
AP	Alkaline phosphatase
ALT (SGPT)	Alanine transaminase (serum glutamic-pyruvic transaminase)
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
APD	Atrial premature depolarization
APD_{50}	Action potential duration at 50% of repolarization
APD_{90}	Action potential duration at 90% of repolarization
ARDS	Adult respiratory distress syndrome
AST (SGOT)	Aspartate transaminase (serum glutamic-oxaloacetic transaminase)
AUC	The area under the plasma concentration curve over dosing interval
AUC_{24h}	The area under the plasma concentration curve from zero to 24 hours, calculated using the linear trapezoidal method.
AUC_{τ}	The area under the plasma concentration curve over the dosing interval pre dose to 12 hours after a single dose, calculated using the linear trapezoidal method.
AUEC	Area under effect curve
AV	Arteriovenous
bid	Two times per day
BL	Baseline
BMT	Bone marrow transplant
BT	Breakthrough
BUN	Blood urea nitrogen
cd	Candela
cd-s	Candela - second
CFU	Colony forming units
CGD	Chronic granulomatous disease
CI	Confidence interval
C_{max}	The maximum observed plasma concentration.
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CT	Computerized tomography
CV	Coefficient of variation
CYP	Cytochrome P450
d	Day
DB	Double blind
DIFI	Documented invasive fungal infection
dL	Deciliter
DOD	Day of death

DRC	Data Review Committee
DSMB	Data Safety Monitoring Board
D/C	Discontinued
ECG	Electrocardiogram
EM	Extensive metabolizer
EORT	End of randomized therapy
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of therapy
ERG	Electroretinogram
est	Estimate
eval	evaluable
F	Bioavailability
FDA	Food and Drug Administration
g	Gram
GI	Gastrointestinal
GvHD	Graft versus host disease
h or hr	Hour
HEM	Heterozygous extensive metabolizer
HERG	Human Ether-a-Go-Go Related Gene
HIV	Human Immunodeficiency Virus
Hz	Hertz
IC_{50}	Inhibitory concentration – that inhibits 50% of growth
ICH	International Conference on Harmonization
I_{kr}	Rapidly activating inward rectifying component of the net delayed rectifier K+ current
IND	Investigational New Drug
IP	Intraperitoneal
IRT	Initial randomized therapy
ITT	Intention to treat
IU	International unit
IV	Intravenous
K_a	Absorption rate constant
kg	Kilogram
K_m	Michaelis-Menten constant describing the concentration at which elimination is half-maximal
L	Liter
L-AMB	Liposomal amphotericin B
LFT	Liver function test
LLN	Lower limit of normal
m	Meter
MC	Multicenter
mEq	Milliequivalent
MFC	Minimum fungicidal concentration
mg	Milligram

MI	Myocardial infarction
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum inhibitory concentration – that inhibits 50% of growth
MIC_{90}	Minimum inhibitory concentration - that inhibits 90% of growth
min	Minute
MITT	Modified intention to treat
mL	Milliliter
mm	Millimeter
mmol	millimole
mmol/L	Millimole/liter
msec	Millisecond
MSG	Mycoses Study Group
µg	Microgram
µmol	Micromole
µM	Micromolar
N or n	Number
NAG	N-acetylglucoseaminidase
NCCLS	National Committee for Clinical Laboratory Standards
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
nm	Nanometer
NOAEL	No observable adverse effect dose level
NR	Not reported
OL	Open label
OLAT	Other licensed antifungal therapy
PD	Pharmacodynamic
PGRD	Pfizer Global Research and Development
PID	Patient identification number
P450	Cytochrome P-450
PK	Pharmacokinetic
PM	Poor metabolizer
PO	By mouth
PP	Per protocol
PSCT	Peripheral stem cell transplant
Q	Intercompartmental clearance
QD	Once daily
QT	Time from beginning of QRS complex to end of T wave in an ECG
QTc	QT interval corrected for heart rate
q 6 h	Every 6 hours
q 8 h	Every 8 hours
q 12 h	Every 12 hours
RBC	Red blood cell
ROC	Receiver operating characteristic

RR	The time between two consecutive R waves in an ECG
SAE	Serious adverse event
SBECD	Sulphobutylether-β-cyclodextrin
SE	Standard error
sec	Second
SLE	Systemic lupus erythematosis
sp	One species
spp	More than one species
tid	Three times a day
T_{lag}	Absorption lag time
T_{max}	The time to first occurrence of C_{max}
UDP	Uridine diphosphate
ULN	Upper limit of normal
USP	United States Pharmacopeia
UV	Ultraviolet
V_c	Central volume of distribution
VERA	Voriconazole Efficacy Response Assessment
V logl functions	Voltage versus log intensity functions
V_p	Peripheral volume of distribution
V_{max}	Maximal elimination capacity
V_{ss}	Volume of distribution at steady state
WBC	White blood cell
wk	Week
yr	year

1 INTRODUCTION

Infections due to *Aspergillus* species are increasing in frequency and are a major cause of morbidity and mortality among immunocompromised patients, particularly those undergoing chemotherapy and bone marrow transplantation for cancer, those with prolonged neutropenia, and patients with graft versus host disease (Groll *et. al.* 1996, Denning 1998, Denning and Stevens 1990,Vartivarian *et. al.* 1993, Andriole 1993, Patterson *et. al.* 2000). Infections due to yeast including *Candida* species also contribute significant attributable mortality in both neutropenic and non-neutropenic patients (Goodrich *et. al.* 1991, Dummer 2000, Collins *et. al.* 1994, Walsh *et. al.* 1991, Walsh *et. al.* 1999, Pizzo 2000). In addition, a growing number of emerging organisms, such as *Fusarium* and *Scedosporium* are being implicated more frequently (Perfect and Schell 1996).

In immunocompromised children, invasive fungal infections carry a poor prognosis and significant mortality, particularly among those with hematological malignancies and chronic granulomatous disease (Walsh *et. al.* 1996; Groll *et. al.* 1999; Winkelstein *et. al.* 2000; Abassi *et. al.* 1999, Shetty *et. al.* 1997).

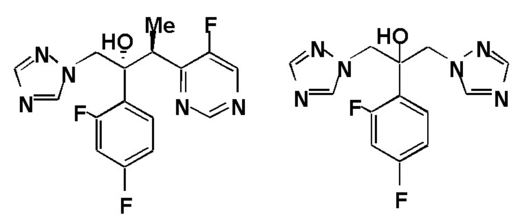
Patients with chemotherapy-induced neutropenia typically require treatment with broad-spectrum antibiotics and multiple other medications. After four to seven days of empirical antibiotic therapy, these patients have an approximately 20% risk of developing fungal infections (Bodey *et al*. 1992; Groll 1996). In this setting, empirical antifungal therapy has been shown to prevent emergence of breakthrough invasive fungal infections and is recommended in the guidelines of the Infectious Diseases Society of America (Rex *et. al.* 2000, Pizzo *et. al.* 1982, EORTC 1989, Walsh *et. al.* 1999).

Amphotericin B remains the standard of care for treating life-threatening fungal infections but is accompanied by significant toxicity and is only available as parenteral therapy. Nephrotoxicity, undesirable infusion-related reactions, electrolyte disturbances, most notably hypokalemia, all contribute to morbidity in amphotericin B-treated patients. The lipid-associated formulations of amphotericin B produce less nephrotoxicity and are generally better tolerated but only available as parenteral formulations. Other agents available include 5-flucytosine and azoles (Stevens *et. al.* 2000). The azoles fluconazole, itraconazole and ketoconazole, offer both oral and intravenous routes of administration but suffer from deficiencies in spectrum, pharmacokinetic profile or toxicity. The therapeutic limitations of the currently available antifungal agents and the increasing prevalence of invasive fungal infections provide impetus for the development of new antifungal agents.

2 Mechanism Of Action

Voriconazole is a second generation triazole and is the result of a discovery program aimed at improving the potency and spectrum of fluconazole. In order to enhance the spectrum, one triazole moiety with a 4-fluoropyrimidine group was substituted and an α methyl group was added to provide fungicidality for *Aspergillus* species and a range of other moulds (Figure 2-1).

Figure 2-1 Structural Similarity of Voriconazole and Fluconazole



Voriconazole Fluconazole

Like other azole antifungals, voriconazole acts by inhibiting the cytochrome P450-dependent 14-α-sterol demethylase required for ergosterol biosynthesis. Voriconazole-treated fungi are depleted of ergosterol and accumulate 14-α-methylated sterols that are thought to disrupt membrane structure and function, thereby inhibiting fungal growth. In the case of *Aspergillus* and some other moulds this mechanism of action also results in death of the organism.

Voriconazole is a highly potent and selective inhibitor of fungal cytochrome P450 enzymes including those of *Aspergillus* spp. Voriconazole has *in vitro* selectivity for fungal as opposed to mammalian sterol and steroid biosynthesis *in vitro.*

3 CLINICAL DEVELOPMENT PROGRAM

3.1 Clinical Pharmacology

The voriconazole clinical program was initiated in Europe in 1991 with dose escalation studies in healthy volunteers. The early Phase I program, therefore, focused on establishing the optimum dosage regimen that would achieve plasma voriconazole concentrations sufficient to cover the MICs of common fungal pathogens. Subsequent studies in the clinical pharmacology program evaluated the effects of renal and hepatic function, food, gender, and age on voriconazole pharmacokinetics, as well as drug interaction studies. Appendix 1 provides details of the pharmacokinetic, pharmacodynamic, pharmacogenetic and drug interaction studies.

3.2 Early Clinical Studies

Appendix 2 provides details of the therapeutic clinical studies. The Dose Ranging Oropharyngeal Candidiasis Study (302) in HIV infected subjects, begun in Europe in 1993, provided basic safety and efficacy data on voriconazole therapy in subjects with fungal infection, as well as dose response information. The clinical program continued in Europe in 1993 with the Chronic Fungal Infection Study (303) which utilized oral therapy and the Non-Comparative Aspergillosis Study (304) which utilized an intravenous loading dose followed by intravenous, and subsequently oral, maintenance therapy.

3.3 Aspergillosis

A US IND for the tablet formulation was filed in 1995. The subsequent submission for the intravenous IND included the protocol for Study 602, to evaluate voriconazole compared to conventional amphotericin B in immunocompromised subjects with acute invasive aspergillosis. A parallel Study 307 had been initiated, led by the European Organization for Research and Treatment of Cancer (EORTC). Pfizer's proposal to conduct a combined analysis of the data from Studies 307 and 602 had been initially discussed with FDA in June 1996. After discussion of a more detailed proposal, agreement with the plan was reached in 1997.

Given the demonstrated efficacy of voriconazole in the Non-Comparative Aspergillosis Study (304), Pfizer submitted an NDA which contained the Non-Comparative Aspergillosis Study (304) together with the contemporaneous Historical Control Study (1003), as support of the efficacy of voriconazole as primary therapy in patients with acute invasive aspergillosis. Following the final Data Review Committee assessments and unblinding of the data, mortality data was submitted to FDA in April, 2001 and a complete study report was filed to FDA in June, 2001. In total, 476 patients with documented *Aspergillus* infection were treated and analyzed for efficacy with voriconazole in the clinical program: 144 patients who received voriconazole as primary therapy in the Global Comparative Aspergillosis Study (307/602) and 332 patients who received voriconazole as primary or salvage therapy from the rest of the program.

3.4 Empirical Therapy

The Empirical Therapy protocol (603/MSG42) was submitted in November 1997. It was agreed with FDA that liposomal amphotericin B would be an appropriate comparative agent and that the voriconazole trial would be similar to MSG32.

3.5 Infections due to Emerging Pathogens

As originally proposed in June 1996 at the first of two End-of Phase II meetings, the efficacy of voriconazole in patients with infections due to emerging pathogens, such as *Scedosporium* and *Fusarium,* would be demonstrated in patients in the Global Rare and Refractory Studies (309 and 604), together with other documented cases from across the voriconazole clinical program.

3.6 Candidiasis

Serious infections due to *Candida* were first studied in the Comparative Esophageal Candidiasis Study (305), in which 200 patients were treated with voriconazole. The results of this study provided evidence of efficacy in *Candida* infections prior to pursuing the study of voriconazole in the treatment of more invasive *Candida* infections, the Global Comparative Candidemia Study (608). The objective of this study is to evaluate voriconazole compared to conventional amphotericin B followed by fluconazole in the treatment of candidemia in non-neutropenic patients was submitted in February 1998 and is ongoing. As of 1 May 2001 (safety cut-off date for this briefing document), 162 of the targeted 426 patients had been enrolled at 52 centers. Results are expected in 2003. A pooled analysis was conducted of 91 completed cases of documented infections with *Candida* from across the program, for inclusion in the November, 2000 NDA. For the purposes of this document, the term “serious *Candida* infections” refers to patients with documented *Candida* infections in this clinical program and the term “serious systemic *Candida* infections” refers to patients with documented non-esophageal *Candida* infections.

3.7 Pediatric Program

Pfizer has also evaluated the potential role for voriconazole in the treatment of serious fungal infections in pediatric patients and has conducted single and multiple dose pediatric pharmacokinetic studies in children two to less than 12 years old, utilizing the intravenous formulation of voriconazole. Therapeutic studies included patients as young as 12 years old, and patients of any age are eligible, under certain circumstances, to receive voriconazole on a compassionate basis.

3.8 Mycology Program

The complementary mycology program utilized Pfizer Laboratories and external reference laboratories: the Medical Mycology Reference Laboratory of the Medical College of Virginia, US, and the Mycology Reference Laboratory of the Public Health Laboratory Service, Bristol, UK.

4 Nonclinical Studies

4.1 Pharmacology/Pharmacodynamics

In a range of general pharmacology studies voriconazole was well tolerated. Minor changes in the QT interval were observed in anesthetized dogs, but not following exposure of dogs to higher plasma concentrations in long term toxicology studies. Also, voriconazole had no effect in *in vitro* assays predictive of effects on cardiac repolarization. Voriconazole can affect phototransduction in the retina in dogs and in humans.

4.2 Pharmacokinetics in Animals

Oral absorption of voriconazole is high (>75%) in all species. The drug has a non-linear elimination profile in all species (including human). Apparent volume of distribution values greater than total body water indicate that voriconazole has some tissue affinity, in keeping with its moderately lipophilic nature. In addition, significant concentrations of voriconazole are obtained in cerebrospinal fluid and the central nervous system of guinea pigs. Clearance of voriconazole is predominantly by hepatic metabolism resulting in several oxidized and further conjugated metabolites. The major circulating metabolite in human, rat and dog is the N-oxide, UK-121,265. In rats, the majority of voriconazole was excreted over 48 hours, with both urine and feces being important routes of elimination. Multiple doses of voriconazole leads to auto-induction of metabolism in rats and mice, but this is not observed in guinea pigs and humans. A comparison of plasma concentrations in humans and animals shows that plasma exposures in toxicology species are similar to those measured at the standard and maximal maintenance doses in patients.

4.3 Toxicology

Voriconazole, given in single doses, was lethal to mice and rats from 300 mg/kg administered orally and from 100 mg/kg administered intravenously. In repeat-dose studies in rats, mice and dogs, the liver was identified as the target organ for toxicity.

Table 4-1 shows the doses at which no adverse effects occur and multiples compared to human exposures on the basis of 24 hour exposure values (AUC_{24h}) for voriconazole and other antifungal agents.

Table 4-1 Daily Therapeutic Dose, No Adverse Effect Dose and Exposure Multiples for Voriconazole and Other Azole Antifungal Agents

	Voriconazole	**Fluconazole**	**Ketoconazole**	**Itraconazole**
Daily Therapeutic Dose	200 mg bid	200 mg QD	200 mg QD	200 mg bid
Weight adjusted total daily dose for a 70kg human (mg/kg)	5.8	2.9	2.9	5.8
Total AUC_{24h} (μg.h/ml) in humans at daily therapeutic dose	39.72	169.5	12	45
NOAEL (mg/kg)	50 (rat) 8 (dog)	100 (rat) 7.5 (dog)	10 (rat) 5 (dog)	40 (rat) 10 (dog)
NOAEL AUC_{24h} (μg.h/ml)	68.4 (rat) 71.8 (dog)	204 (dog)	20 (dog)	44.9 (dog)
Estimated exposure multiple*	1.7 (rat)	1.2 (dog)	1.7 (dog)	1.0 (dog)

NOAEL = no observable adverse effect level
*Calculated as the lower value of the dog or rat NOAEL AUC_{24h}/human AUC_{24h}

In the 24-month carcinogenicity studies, hepatocellular adenoma appeared in male and female mice at 100 mg/kg and in female rats at 50 mg/kg. An increased incidence of hepatocellular carcinoma was evident in male mice only at 100 mg/kg. Hepatocellular adenoma and carcinoma, as well as non-neoplastic changes (foci of cellular alteration) are known to occur in rodents after chronic administration of hepatic enzyme inducers and should, therefore, not be extrapolated to humans. Thus, no carcinogenic risk to man is predicted from these rodent studies.

In reproduction studies, voriconazole produced adverse effects on parturition and was teratogenic in rats. Voriconazole was not mutagenic or clastogenic.

Following the observation of visual disturbances in volunteers and patients, special attention was given to ophthalmology investigations in the toxicology program. No unusual findings in rats (24 months), mice (24 months) or dogs (12 months) have been noted. The postmortem examination in these studies covered all major structures and no histopathological evidence of toxicity to the visual pathways was observed. Counting the nuclear layers in the retina of rats and dogs treated for up to 24 and 12 months, respectively, did not reveal differences compared to the control group.

The number of cell nuclei which touch the line drawn perpendicularly to the retinal circumference were counted. Analysis of the inner and outer nuclear layer cell counts revealed no differences between treated and control animals.

As voriconazole has limited aqueous solubility, a solubilizing excipient, sulfobutylether-β-cyclodextrin (SBECD), is the solubilizing agent in the intended commercial intravenous formulation. The excipient SBECD was evaluated in a toxicology program and studies in healthy volunteers characterized its pharmacokinetics and tolerability. SBECD, in the intravenous toxicology program, had a low acute toxicity, the minimal single lethal dose being above 2000 mg/kg. Repeat-dose studies identified renal tubular vacuolation and foamy macrophages in multiple organs as most noteworthy findings in all species. Obstruction of renal tubules and single cell necrosis in the liver of rats at and above 3 g/kg indicate borderline toxicity in these organs, both findings being a consequence of massive cellular vacuolation. At this high dose there was a slight renal functional impairment as evidenced by small increases in urea and creatinine (<20% greater than controls). Doses of 1000 mg/kg for one month and 600 mg/kg for six months did not produce functional renal changes. In dogs the highest dose of 1.5 g/kg did not produce histopathological evidence of toxicity. In continuous infusion studies at doses of 3 and 10 g/kg, the renal effects produced by SBECD were those expected from the bolus injection studies.

5 Microbiology

5.1 *In Vitro* Activity of Voriconazole

Voriconazole has broad *in vitro* antifungal activity against yeasts and moulds, including a wide range of less common pathogens. Voriconazole is active against the primary opportunistic fungal pathogens (*Aspergillus* spp., *Candida* spp. and *Cryptococcus* spp.), common dermatophytes (*Trichophyton* spp. and *Microsporum* spp.) and the fungi which cause endemic mycoses (*Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*) (Espinel-Ingroff, 1999; Manavathu, 1997; Sutton, 1999; Hoban, 1999; Cuenca-Estrella, 1999; Sanati, 1997; Pfaller, 2000; Barry, 2000; Ruhnke, 1997; Perea, 2001; Li, 2000). Voriconazole is also active against a wide range of less frequently encountered fungal pathogens including *Fusarium* spp., *Acremonium kilensii, Scedosporium apiospermum, S. prolificans, Trichosporon* species and *Pseudallescheria boydii* (asexual form of *S. apiospermium)* (Espinel-Ingroff, 2001; Cuenca-Estrella, 1999). Voriconazole is fungicidal *in vitro* against all *Aspergillus* spp. and a range of moulds such as *Scedosporium spp.* and *Fusarium spp*., which have limited susceptibility to available antifungal agents.

Table 5-1 provides a summary of published drug-specific MIC_{90} and MFC ranges for the clinically important filamentous fungi according to the NCCLS M38P method (Espinel-Ingroff A, *et al*. 2001).

Table 5-1 Voriconazole *in vitro* Activity (Minimum Inhibitory Concentration [MIC_{90}] and Minimum Fungicidal Concentration [MFC]) against Moulds

Organism	Number of Isolates	Antifungal Agent	MIC_{90} Range (µg/mL)	MFC Range (µg/mL)
Aspergillus species	479	Voriconazole	0.25 – 8	0.5 – 32
		Amphotericin B	0.5 – 4	0.12 – 16
		Itraconazole	0.25 –2	0.12 – 32
Fusarium solani	65	Voriconazole	2 - >8	2.0 - ≥16
	65	Amphotericin B	1.0 – 4	0.5 - >8
	54	Itraconazole	>16	>16
Scedosporium apiospermum (Pseudallescheria boydii)	54	Voriconazole	0.5	0.25 - >16
		Amphotericin B	8	4 - >16
		Itraconazole	2 - 4	1.0 - >16
Scedosporium prolificans	28	Voriconazole	>8	2 - >8
		Amphotericin B	>8	8
		Itraconazole	>8	NR

NR = not reported
NCCLS M38P Method, no established breakpoints for *Aspergillus* or other filamentous fungi (NCCLS 1998)

Voriconazole has potent *in vitro* inhibitory activity against isolates of *Aspergillus* species, *Fusarium* species, *Scedosporium* species and *Candida* species.

Table 5-2 provides a summary of published voriconazole and comparator antifungal MIC_{90} ranges for *Candida* determined by the NCCLS M27A method (Espinel-Ingroff A, *et al*. 2001). Table 5-3 shows the NCCLS interpretive guidelines for susceptibility testing *in vitro* of *Candida* species.

Table 5-2 Voriconazole *in vitro* Activity (MIC_{90}) against Yeasts*

Organism	Number of Isolates	Antifungal Agent	MIC_{90} Range (µg/mL)
Candida species	3,664	Voriconazole	<0.03 - >16
		Fluconazole	0.5 - >128
		Amphotericin B	0.12 – 2
		Itraconazole	0.12 - >8
		Ketoconazole	≤0.12 - 4
		Flucytosine	≤0.12 - 4

NR = not reported
*NCCLS M27A Method (NCCLS 1997, Rex *et. al.* 1997)

Table 5-3 Interpretive Guidelines for Susceptibility Testing *in vitro* of *Candida* Species**

Antifungal Agent	Susceptible	Susceptible – dose dependent	Intermediate	Resistant
Fluconazole*	≤8	16 – 32	-	≥64
Itraconazole	≤0.125	0.25 – 0.5	-	≥1
Flucytosine	≤4	-	8 – 16	≥32

*Isolates of C. krusei are assumed to be intrinsically resistant to fluconazole and their MICs should not be interpreted this scale.
**NCCLS M27A, 1997

5.2 *In Vivo* Activity of Voriconazole

Consistent with its *in vitro* potency and broad-spectrum, voriconazole is highly effective *in vivo* against disseminated and pulmonary aspergillosis, invasive candidiasis and pulmonary and central nervous system cryptococcosis in both immunocompetent and immunocompromised guinea pigs. The guinea pig model was chosen because the metabolism of voriconazole is similar to that in humans. In mice, autoinduction occurs and, therefore, this model is inappropriate for study of the *in vivo* activity of voriconazole. Guinea pigs were chosen because they are an established model for testing azoles, including itraconazole, and since the voriconazole pharmacokinetic characteristics in this species are similar to those in humans. In models of invasive systemic fungal disease, animals are rendered neutropenic by treatment with cyclophosphamide and further immunosuppressed with corticosteroids. Inocula large enough to produce rapidly fatal or widely disseminated disease are injected intravenously and a variety of antifungal regimens are tested between four and seven days post-infection. Efficacy was assessed on the basis of animal survivors and/or reductions in the fungal burden in tissues at the time of sacrifice.

Two specific studies evaluated the activity of voriconazole in disseminated invasive aspergillosis (Kirkpatrick *et al*., 2000) and in disseminated *Candida krusei* (Ghannoum *et al.*, 1999) and are described in more detail.

5.2.1 Animal Model of Disseminated Invasive Aspergillosis

Five groups of eight to ten male Hartley guinea pigs were immunosuppressed with daily subcutaneous triamcinolone (20mg/kg) injections and rendered neutropenic with a single intraperitoneal dose of cyclophosphamide (300mg/kg) (Kirkpatrick *et. al.*, 2000). The animals were challenged intravenously with a lethal inoculum of 10^6 *A. fumigatus* conidia. Antifungal therapy was begun 24 hours thereafter and continued for five days. Organ culture was performed after sacrifice (96 hours post last dose). Semiquantitative results are depicted in Table 5-4.

Table 5-4 Semiquantitative Results of Organ Culture of Invasive Aspergillosis in Immunocompromised Guinea Pigs

Treatment group	Dose (mg/kg/day)	Colony count [mean $\log_{10}$ colony forming units/g of tissue] ± SE			
		Liver	Lung	Kidney	Brain
		Count	Count	Count	Count
Control	0	3.44±0.4	1.00±0.2	3.35±0.2	3.11±0.2
Voriconazole	10	0.18±0.1	0.18±0.2	0.26±0.1	0.09±0.1
Voriconazole	5	0.16±0.1	0.51±0.1	0.38±0.1	0.25±0.1
Itraconazole	10	0.65±0.4	0.11±0.1	0.85±0.3	0.30±0.2
Itraconazole	5	1.36±0.3	0.73±0.1	1.62±0.4	1.09±0.4
Amphotericin B	1.25	0.89±0.5	0.25±0.2	0.53±0.4	0.89±0.6

SE = standard error
Source: Kirkpatrick *et al*., Antimicrobial Agents and Chemotherapy, 2000,44:2865-2868

5.2.2 Animal Model of Disseminated *Candida krusei* Infection

Five groups of eight (treatment groups) or 14 (control) male Dunkin Hartley albino guinea pigs were immunosuppressed with daily oral dexamethasone (2mg/kg) and rendered neutropenic with two intraperitoneal injections of cyclophosphamide (100mg/kg each) on Days 1 and 4. (Ghannoum *et. al*., 1999) On Day 5, the animals were challenged with an intravenous inoculum of *Candida krusei* suspension containing10^8 CFU/guinea pig. This inoculum produced infection in the kidneys, liver and brain in earlier studies. Antifungal therapy was begun one hour thereafter and continued for 7 days with amphotericin B at 1 mg/kg ip once daily at alternate days, fluconazole 20 mg/kg orally q 12 h, voriconazole at 5 mg/kg orally q 12 h or voriconazole 10 mg/kg orally q12 h. Organ culture from brain, liver and kidneys was performed after sacrifice (1 day post last dose). Semiquantitative results are depicted in Table 5-5.

Table 5-5 Semiquantitative Results of Organ Culture of Hematogenous *Candida krusei* Infections in Immunocompromised Guinea Pigs

Treatment group	Dose (mg/kg/day)	Colony count [mean $\log_{10}$ colony forming units/g of tissue] ± SE		
		Liver	Kidney	Brain
		Count	Count	Count
Control	0	2.00±1.4	1.80±0.8	3.30±0.3
Voriconazole	10	0.50±0.1	0.70±0.4	1.10±0.7
Voriconazole	5	0.72±0.5	0.27±0.1	1.20±1.7
Fluconazole	20	1.70±0.4	1.40±0.2	2.90±0.4
Amphotericin B	1	1.60±0.9	1.40±0.2	3.30±0.1

SE = standard error
Source: Ghannoum *et al*., J Chemotherapy, 1999,11:34-39

5.3 Summary

Voriconazole demonstrates *in vitro* potency and cidality (minimum fungicidal concentrations approximately two times minimum inhibitory concentrations) against certain moulds and emerging pathogens, including *Aspergillus* spp. and *in vitro* potency against yeast, including *Candida krusei*. Voriconazole was highly efficacious in comparative studies using guinea pig models of invasive aspergillosis and candidiasis. These data indicate that the potent, broad-spectrum antifungal activity observed *in vitro* with voriconazole translates to efficacy in neutropenic animal models of aspergillosis and candidiasis.

6 Clinical Pharmacology

6.1 Overview

The voriconazole clinical pharmacology program was initiated in Europe in 1991 with dose escalation studies in volunteers. It includes 1,150 subjects from 58 Phase 1 studies (see Appendix 1). Healthy subjects and special populations relevant to the clinical use of voriconazole have been studied (Table 7-1). A population approach was applied to the analyses of Phase 1 pharmacokinetic data from a heterogeneous mixture of subjects. This analysis complemented the specific studies in special populations and explored the effect of multiple factors that could influence the pharmacokinetics of voriconazole. The clinical pharmacology program provided explanations for the inter-individual variability in voriconazole pharmacokinetics and, therefore, the rationale for whether voriconazole dose adjustments are required in specific clinical situations and special populations, as described in Table 6-1.

Table 6-1 Subpopulations and Factors Investigated in the Clinical Pharmacology Program

Demography	Organ dysfunction	Interactions	Patients
• Age • Sex • Race (Caucasian/Japanese) • CYP2C19 genotype • Body weight	• Hepatic impairment • Renal impairment • Renal failure requiring hemodialysis	• Enzyme induction • Enzyme inhibition • Gastric pH increase • High fat meals • Alcohol consumption[1] • Cigarette smoking[1]	• Adult patients at risk of fungal infection • Immunocompromised children

[1]Investigated in population pharmacokinetics only and found not to influence voriconazole pharmacokinetics

Potential pharmacokinetic interactions with voriconazole were characterized both *in vitro* and *in vivo*, resulting in generation of specific dosing guidance for prescribing physicians.

Table 6-2 describes the number of subjects in the clinical pharmacology program used in the various pharmacokinetic analyses.

Table 6-2 Subjects in the Voriconazole Clinical Pharmacology Program in Various Analyses

Phase 1 Population	N	Presentation
Total population Includes supportive studies not evaluated for pharmacokinetics	1150	Subject numbers and dosing described by study in Appendix 1
Total population evaluated for pharmacokinetics Includes pharmacokinetics of other drugs in drug interaction studies	913	C_{max}/AUC/T_{max} summaries for individual studies, including parameters for other drugs in drug interaction studies
Population included in population pharmacokinetic analysis All doses, IV and oral, including voriconazole treatment only periods of drug interaction studies. Subjects without genotype data excluded. Data available up to NDA submission.	236	All presentations on population pharmacokinetics, influence of genotype on pharmacokinetics in a subset of subjects given 200 mg q 12 h.

6.2 Formulations

Voriconazole is available as oral tablets or intravenous formulation. The high bioavailability of the oral formulation allows switching between the formulations as required by the clinical situation (Sec. 6.8).

As voriconazole has limited aqueous solubility, a solubilizing excipient, sulfobutylether-β-cyclodextrin (SBECD), was used in the intravenous formulation in clinical trials beginning in 1994, and is the solubilizing agent in the intended commercial intravenous formulation. The excipient SBECD was evaluated in a toxicology program and studies in healthy volunteers characterized its pharmacokinetics and tolerability.

Voriconazole for infusion is supplied in one dosage strength and product configuration, nominally 200 mg of voriconazole in a 30 ml vial. After reconstitution, the product contains 10 mg/ml of voriconazole, 160 mg/ml of SBECD and Water for Injection (USP).

The 50 mg intended commercial tablet is a standard round convex white film-coated tablet and the 200 mg intended commercial tablet is a capsule shaped white film-coated tablet.

6.3 Absorption

Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved one to two hours after dosing in the fasted state. The oral bioavailability of voriconazole is estimated to be 96%. Multiple dosing with the intended commercial tablet formulation of voriconazole with high fat meals reduces the C_{max} and AUC_{τ} by 34% and 24%, respectively, compared with administration in the fasted state. It is recommended that voriconazole be given at least one hour before or one hour following a meal. The absorption of voriconazole was not affected by changes in gastric pH induced by treatment with a histamine H_2 receptor antagonist (ranitidine).

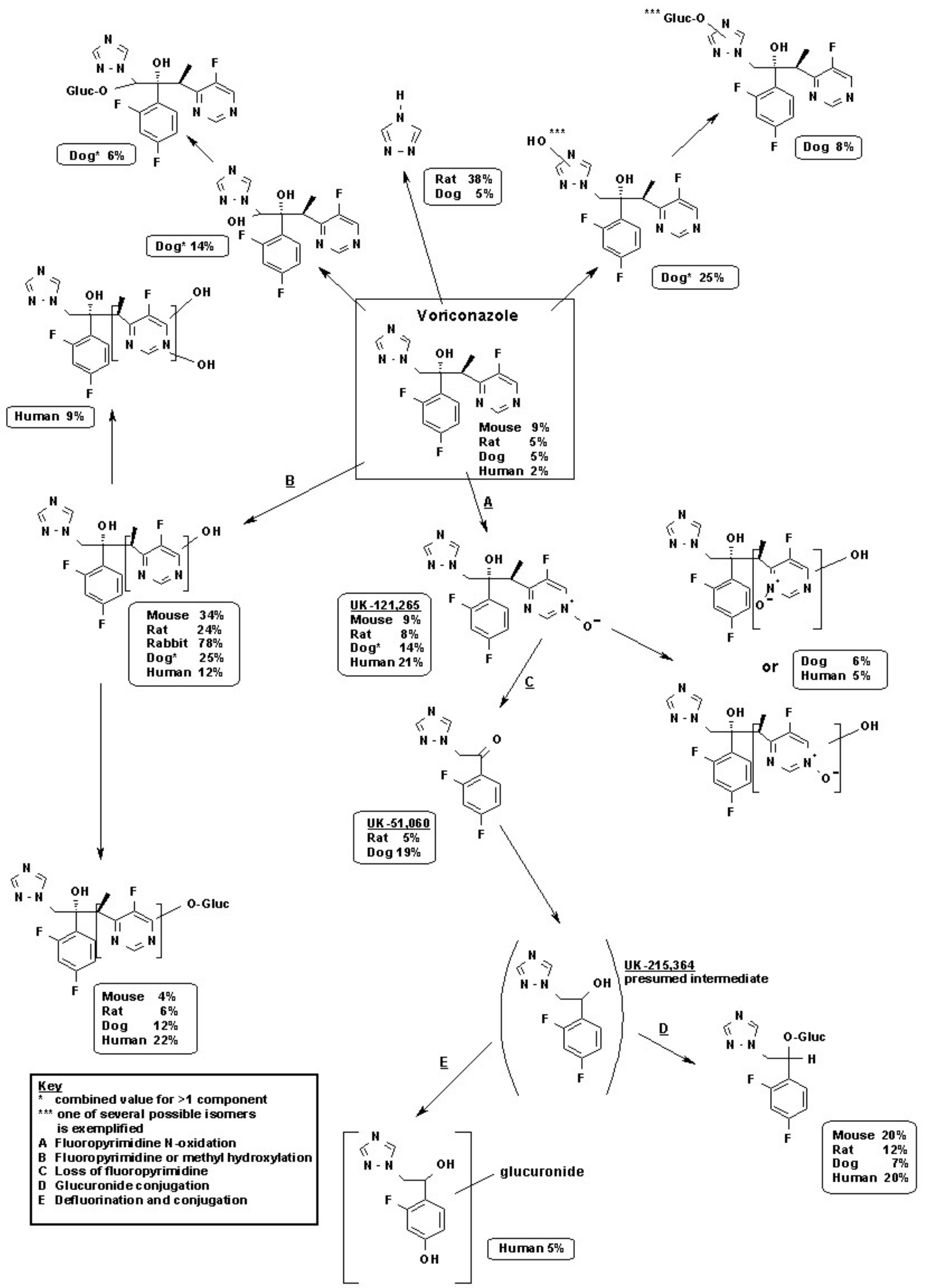
6.4 Distribution

The volume of distribution at steady state (V_{ss}) of voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Voriconazole is moderately bound to plasma proteins at 58%. Voriconazole has been detected in cerebrospinal fluid, sampled in some patients in the compassionate use studies. The mean voriconazole concentration in the cerebrospinal fluid from seven patients was 1.16 μg/ml. Voriconazole was also detected in post-mortem samples of liver, kidney, lung, heart, brain and spleen. Wide distribution of voriconazole in tissues is consistent with data from animal studies.

6.5 Elimination

Voriconazole is eliminated primarily by hepatic metabolism, with less than 2% of a radiolabelled dose excreted as unchanged drug. In the Radiolabelled Oral and IV Study (220), 80% of the dose was excreted in the urine, almost exclusively as metabolites, and 24% was found in the feces following intravenous administration. Similarly, following oral administration 84% of the dose was excreted in urine and 22% in feces. The majority of radioactivity (94.7% IV; 94.4% oral) was eliminated within 96 hours. Eight metabolites of [^{14}C]-voriconazole were identified, all of which were present in urine, and two were present in feces. The primary route of metabolism involved N-oxidation of the fluoropyrimidine ring to form UK-121,265 which accounted for 72% of the circulating radiolabelled metabolites one hour post-dose during multiple dosing. Approximately 21% of the radiolabelled dose of voriconazole was excreted in urine as UK-121,265. Other major metabolites detected in urine, each constituting more than 15% of the dose, were glucuronide conjugates. UK-121,265 undergoes further metabolism as shown in Figure 6-1.

Figure 6-1 Major Metabolites of Voriconazole (As Percent of Dose) Following Multiple Administration of [^{14}C]-Voriconazole To Mouse, Rat, Rabbit, Dog and Human



Voriconazole was shown to be metabolized by CYP2C19, CYP2C9 and CYP3A4 in *in vitro* studies using human liver microsomes and microsomes prepared from genetically engineered cell lines expressing specific cytochrome P450 enzymes. Each of these iso-enzymes contributes to the formation of the major, N-oxide metabolite, UK-121,265. However, the affinity of voriconazole for CYP3A4 is 100-fold lower than that for CYP2C9 and CYP2C19. UK-121,265 was identified as the major circulating plasma metabolite in humans, rats and dogs**.** UK-121,265 displays minimal antifungal activity compared to voriconazole in *in vitro* fungal susceptibility tests. The metabolite does not display affinity for a wide range of physiological receptors or binding sites and had no significant effects in *in vitro* assays for QTc prolongation (as assessed in dog isolated Purkinje fibers and HERG binding assays) (See Safety: Cardiac Function). Therefore UK-121,265 is unlikely to contribute to the efficacy and safety profile of voriconazole.

6.6 Non-Linear Pharmacokinetics

Voriconazole exhibits non-linear pharmacokinetics due to saturation of its metabolism. A greater than proportional increase in exposure is observed with increasing intravenous or oral doses. Because of the non-linear pharmacokinetics, the apparent terminal half-life is dose-dependent and is not predictive of the accumulation or elimination of voriconazole. In a population pharmacokinetic analysis of data from 11 Phase 1 studies (236 subjects with CYP2C19 genotype data), plasma voriconazole concentration-time data were most appropriately described by a two-compartment disposition model with non-linear elimination characterized in terms of V_{max} (the maximal elimination capacity) and K_m (the Michaelis-Menten constant describing the concentration at which elimination is half-maximal). Population pharmacokinetic parameter estimates, based on data from 236 subjects are shown in Table 6-3.

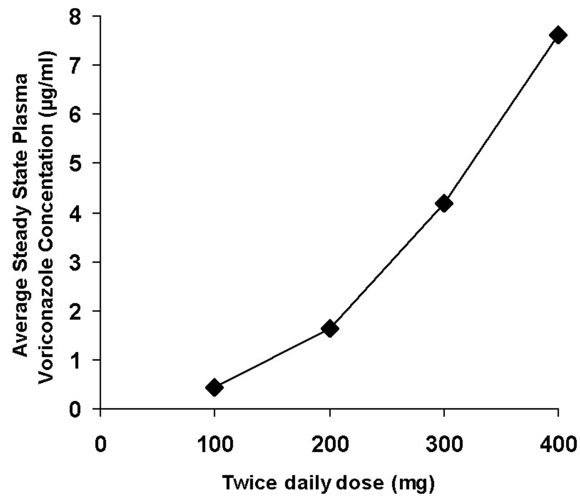
Table 6-3 Population Pharmacokinetic Parameter Estimates for Voriconazole

Parameter	**Units**	**Estimate (%CV)***
Bioavailability, F	%	96 (13)
Absorption rate constant, K_a	/h	0.654
Absorption lag time, T_{lag}	h	0.19 (60)
Central volume of distribution, V_c	L/kg	0.88 (13)
Peripheral volume of distribution, V_p	L/kg	3.74 (38)
Intercompartmental Clearance, Q	L/h	33.7
K_m, EM K_m, HEM K_m, PM	μg/ml	0.404 0.463 1.30
V_{max}, EM males V_{max}, HEM males V_{max}, PM males	μg/h	28400 24900 23300
V_{max}, EM females V_{max}, HEM females V_{max}, PM females	μg/h	26696 18675 17475

CV = coefficient of variation; EM= extensive metabolizer, HEM = heterozygous extensive metabolizer, PM = poor metabolizer
*Overall CV for K_m and V_{max} were 79% and 23% respectively.

The population pharmacokinetic model predicts an increase in average steady-state plasma voriconazole concentration from 1.66 μg/ml to 4.19 μg/ml, a 2.5 fold increase, when the oral dose increased 1.5 fold from 200 mg q 12 h to 300 mg q 12 h (Figure 6-2). When intravenous dosing of 3 mg/kg q 12 h is increased by 1.3 fold to 4 mg/kg q 12 h, average steady-state plasma voriconazole concentration is predicted to increase 2.3 fold from 1.82 µg/ml to 4.20 µg/ml.

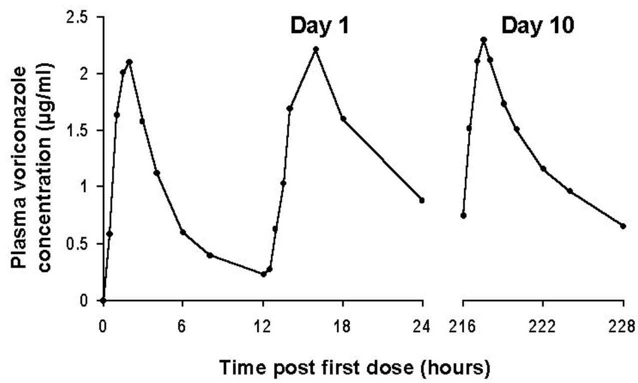
Figure 6-2 **Steady-State Plasma Voriconazole Concentrations during Multiple oral Dosing, Predicted from the Population Pharmacokinetic Model**.



6.7 Pharmacokinetics from Use of Loading Dose Regimen

Voriconazole does not reach steady state plasma concentrations until Day 6 in healthy volunteers when administered at 200mg orally q 12 h without a loading dose. Use of a loading dose regimen (two doses of 6mg/kg IV or 400mg orally 12 hours apart) achieves plasma concentrations close to steady state on the first day of dosing. Figure 6-3 displays the plasma concentrations of Day 1 (n = 17) after two oral loading doses of 400 mg q 12 h and Day 10 (n = 17) after maintenance dosing with oral voriconazole administered at a dose of 200 mg q 12 h.

Figure 6-3 Loading Dose Study (247) - Mean Plasma Voriconazole Concentrations on Day 1 and at Steady State, Day 10



The loading dose evaluated in this study is the recommended Day 1 dose regimen in the proposed label. Once steady state is achieved, exposure to voriconazole does not change over 30 days of dosing in healthy subjects.

6.8 Switching from Intravenous to Oral Dosing

The pharmacokinetic consequences of switching maintenance treatment from intravenous to oral administration were investigated in Multiple Dose Escalation IV/Oral Switch Study (230). All subjects received two loading doses of 6mg/kg delivered by intravenous infusion over 2 hours at 12 hour intervals on the first day. Thereafter subjects received one of three maintenance doses of 3, 4 or 5mg/kg IV, given over 60 minutes q 12 h for six days, then switched to an oral dosing regimen of 200, 300 or 400mg q 12 h, respectively for a further seven days. Pharmacokinetic profiles were determined on the final day of each period of maintenance treatment.

The weight range of subjects in this study was 66 kg to 91 kg. Table 6-4 displays the actual intravenous dose received by these subjects and the AUC_{τ} ratio between oral and intravenous administration, with 95% confidence intervals.

Table 6-4 Multiple Dose Escalation IV/Oral Switch Study (Study 230) – Actual Intravenous Doses of Voriconazole Received

	N	Weight Mean kg (range)	Range of actual IV dose (mg)	Oral/IV AUC_{τ}Ratio (%)	95% CI
3 mg/kg IV q 12 h/200mg oral q 12 h[1]	14	79 (66 – 91)	198 – 276	70.2	61, 81
4 mg/kg IV q 12 h/300mg oral q 12 h[2]	7	73 (68 – 83)	272 – 331	105.0	78, 142
5 mg/kg IV q 12 h/400mg oral q 12 h[1]	14	79 (66 – 91)	323 - 450	88.2	77, 102

[1]Cohort 1
[2]Cohort 2

The comparative mean data from Day 6 of each period of maintenance treatment are presented in Table 6-5.

Table 6-5 Multiple Dose Escalation IV/Oral Switch Study (Study 230) - Mean Pharmacokinetic Data at Steady State

Pharmacokinetic Parameter*	Voriconazole Dose Regimen					
	3mg/kg IV q 12 h → 200mg oral q 12 h		4mg/kg IV q 12 h → 300mg oral q 12 h		5mg/kg IV q 12 h → 400mg oral q 12 h	
	IV	Oral	IV	Oral	IV	Oral
C_{max} (µg/ml)	3.00	1.89	5.40	4.84	7.18	5.31
AUC_τ(µg.h/ml)	13.92	9.77	29.47	30.94	43.37	38.25
T_{max} (h)	1.07	1.50	1.04	1.43	1.02	1.81

*Adjusted means are geometric for AUC_τ,and C_{max} and arithmetic for T_{max}

These data show that the average C_{max} and AUC_τ of voriconazole during intravenous dosing at 3mg/kg q 12 h is higher than that observed with oral maintenance dosing with 200mg q 12 h. This can be partly explained by the discrepancy between the oral dose and the actual intravenous dose (total in mg) received (Table 6-4).

A series of simulations were performed to characterize the pharmacokinetics of the switch strategy, based on the population pharmacokinetic model derived from a larger, more heterogeneous population. This population, which included subjects in the Multiple Dose Escalation IV/Oral Switch Study (Study 230), also included males, females, elderly and young, Japanese and Caucasians subjects from 10 other Phase 1 studies, with an observed weight range of 51 to 97kg. The simulations found close agreement in AUC values for the alternative maintenance doses of 200mg oral q 12 h or 3mg/kg IV q 12 h and 300mg oral q 12 h or 4mg/kg IV q 12 h, although differences may be evident at the extremes of the weight range in the higher dose group (300mg or 4mg/kg). Therefore it is appropriate to switch between oral and intravenous dosing when this is clinically indicated**.** In all clinical studies utilizing both intravenous and oral formulations, switch between formulations was permitted.

6.9 Investigation of Pharmacokinetic Variability

The inter-individual variability of voriconazole pharmacokinetics is high. The coefficients of variation (CV) of the average steady state plasma voriconazole concentration predicted from the Phase 1 population pharmacokinetic model during administration of 200mg orally or 3mg/kg intravenously q 12 h were 94% and 100%, respectively. In contrast, the intra-individual variability in voriconazole pharmacokinetics is low. Residual variability (which includes intra-subject variability) was 33% and 19% for oral and intravenous dosing, respectively. The inter-individual coefficient of variation of the average plasma voriconazole concentration in patients from Therapeutic Studies was 88%. Pharmacokinetic data from the Therapeutic Studies are described in Appendix 8.

6.9.1 CYP2C19 Genotype

Studies in healthy subjects showed that CYP2C19 plays a key role in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism, which divides the population into poor metabolizers and extensive metabolizers as a result of critical point mutations in the gene encoding the protein of CYP2C19 (Goldstein and de Morais, 1994). Extensive metabolizers are further divided into homozygous metabolizers and heterozygous metabolizers. The distribution of CYP2C19 genotypes in different racial groups is presented in Table 6-6.

Table 6-6 Observed Frequencies of CYP2C19 Genotypes in Different Racial Groups

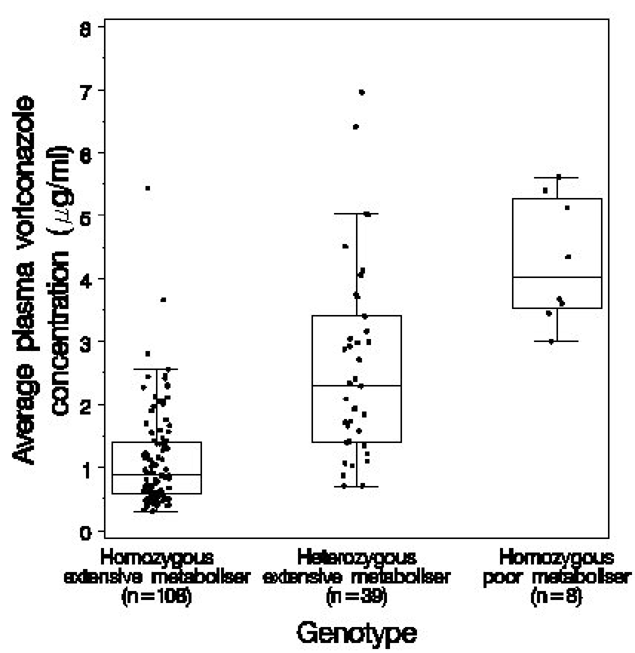
Genotype	Caucasian[1] %	Blacks[2] %	Japanese[3] %	Chinese[4] %
PM	2	2	19	14
HEM	26	28	46	43
EM	73	70	35	43

PM = poor metabolizers; HEM = heterozygous metabolizers; EM = extensive metabolizers
[1]Xie, et. al., 1999
[2]Marinac, et. al., 1996
[3]Kubota, et. al., 1996
[4]Xie, 2000.

A similar prevalence of poor metabolizers is found in black and Caucasian American populations (Marinac *et al.* 1996). The Asian population, including Japanese, generally has a higher proportion of poor metabolizers, constituting approximately 15 to 20% of the population (Kubota, *et. al.*,1996).

The influence of genotype on average steady-state plasma voriconazole concentration following a dose of 200 mg q 12 h in 155 healthy subjects from the population pharmacokinetics dataset is shown in Figure 6-4.

Figure 6-4 Influence Of CYP2C19 Genotype on Average Steady-State Plasma Voriconazole Concentrations* - Population Pharmacokinetics Analysis Population



***Box and whisker plots** display the box locations of the median, upper and lower quartiles, with whiskers extending to the furthest data point within 1.5 times the inter-quartile range. Scatter of individual data also displayed.

The population pharmacokinetic analysis of Phase 1 data showed that poor metabolizers have, on average, four-fold higher voriconazole levels than their extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have on average two-fold higher voriconazole exposure than their extensive metabolizer counterparts. However, there is considerable variability in voriconazole exposure within each genotype and overlap in exposure across genotypes. Of note, genotype information was not captured in the clinical program.

6.9.2 Gender and Age in Adults

The influence of age and gender on the pharmacokinetics of voriconazole was investigated in the Male/Female and Young/Elderly Study (250). This was an open, parallel group study in which groups of young (18-45 years) and elderly (>65 years) males and females initially received a single intravenous dose of 6 mg/kg voriconazole infused over 60 minutes. After a seven day washout, they were given 400 mg orally q 12 h for one day, followed by 200mg q 12 h for 5.5 days. Multiple-dose pharmacokinetic parameters are presented in Table 6-7.

Table 6-7 Male/Female and Young/Elderly Study (250) -Multiple-Dose Pharmacokinetic Parameters In Healthy Young Subjects And Healthy Elderly Subjects

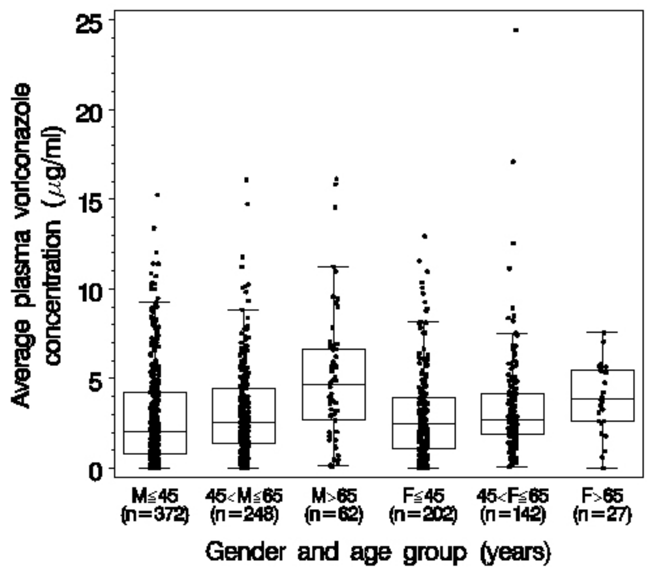
Parameter	Young males (N = 18)	Elderly males (N = 17)	Young females (N = 17)	Elderly females (N = 17)
C_{max} (µg /ml)	2.16	3.47	3.96	3.27
AUC_τ (µg.h/ml)	13.59	25.24	28.88	21.89
T_{max} (h)	1.58	1.38	2.00	1.41

Geometric mean AUC_τ and C_{max}, arithmetic mean T_{max}

C_{max} and AUC_τ for young healthy females were 83% and 113% higher, respectively, than in young healthy males. No significant differences in C_{max} and AUC_τ were observed between healthy elderly males and healthy elderly females . C_{max} and AUC_τ in elderly healthy males were 61% and 86% higher, respectively, than in young healthy males. No significant differences in C_{max} and AUC_τ were observed between elderly healthy females and young healthy females.

The population pharmacokinetic analysis of Phase 1 data confirmed age and gender as independent influences on voriconazole clearance, but less important than genotype. No dosage adjustment was made on the basis of age or gender in the therapeutic studies. In contrast to the Phase 1 data, pharmacokinetic data collected in the therapeutic studies did not show any difference in exposure between males and females (Figure 6-5).

Figure 6-5 Plasma Voriconazole Concentrations in Individual Patients by Gender and Age Group* -Therapeutic Studies



*Box and Whisker plots display the box locations of median, upper and lower quartiles, with whiskers extending to the furthest data point within 1.5 times the inter-quartile range. Scatter of individual data also displayed. Average plasma concentrations were calculated over the duration of therapy.

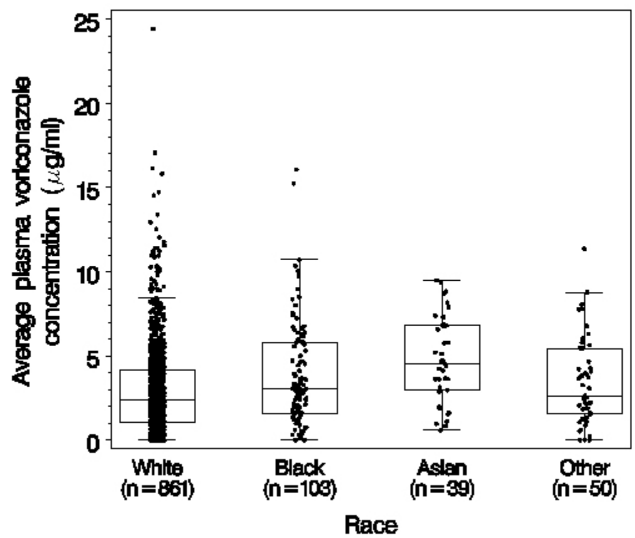
Exposure in the elderly population (> 65 years) in these studies was higher than in subjects aged 45 years or less. However, safety analyses showed that higher exposure in the elderly was not associated with increased reporting of adverse events. Therefore, no dosage adjustment is recommended for the elderly or females.

6.9.3 Race

The Phase 1 population pharmacokinetic analysis investigated the effect of race on voriconazole pharmacokinetics. The analysis included 65 Asians, of whom 64 were Japanese subjects, in the total population of 236 subjects (see Table 6-3). Only four subjects included in the analysis were black. After accounting for CYP2C19 genotype and body size, the model used in this population did not identify race as an influence on the pharmacokinetics of voriconazole.

In addition, pharmacokinetic data collected in the therapeutic studies were analyzed by race and are summarized in Figure 6-6.

Figure 6-6 Plasma Voriconazole Concentrations in Individual Patients by Race* – Therapeutic Studies



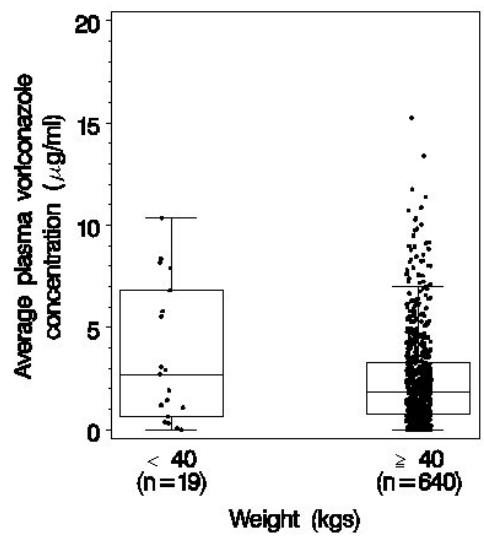
*Box and Whisker plots display the box locations of the median, upper and lower quartiles, with whiskers extending to the furthest data point within 1.5 times the inter-quartile range. Scatter of individual data also displayed. Average plasma concentrations were calculated over the duration of therapy.

The highest median average plasma concentration was observed in Asian patients. Although the number of Asian subjects was low, this finding is consistent with the higher prevalence of CYP2C19 poor metabolizers in the Asian population. Genotype data was not collected in the therapeutic studies. The plasma voriconazole concentrations in the 103 black patients did not appreciably differ from the concentrations in the 861 white patients.

6.9.4 Body Weight

Several simulations were performed using the population pharmacokinetic model derived from Phase 1 data to explore the relationship between body weight, dosing and AUC. In general, the model predicted that for oral dosing, subjects who weighed less would have higher AUC values than subjects who weighed more. In the therapeutic studies, the oral voriconazole dose was halved for subjects below 40 kg. Only 28 of 1214 patients in the Therapeutic Studies population (2.3%) weighed less than 40 kg. Plasma voriconazole concentrations observed during oral dosing in patients above or below 40 kg is shown in Figure 6-7.

Figure 6-7 Plasma Voriconazole Concentrations in Subjects <40 kg in Weight and ≥40 kg in Weight During Oral Dosing – Therapeutic Studies*



*Box and Whisker plots display the box locations of the median, upper and lower quartiles, with whiskers extending to the furthest data point within 1.5 times the inter-quartile range. Scatter of individual data also displayed. Average plasma concentrations were calculated over the duration of therapy.

Exposure in patients less than 40 kg was within the range observed in patients weighing greater than 40 kg. This suggests that the therapeutic strategy to half the oral dose in patients under 40 kg succeeded in achieving plasma voriconazole concentrations comparable to those in patients above 40 kg.

6.9.5 Hepatic Impairment

The single-dose pharmacokinetics of voriconazole were studied in subjects with chronic stable hepatic impairment (Child-Pugh classes A and B), Single Dose Hepatic Impairment Study (238). After a single oral dose of voriconazole, AUC was 233% higher in subjects with mild to moderate hepatic cirrhosis compared with subjects with normal hepatic function. Given the non-linear pharmacokinetics of voriconazole, the difference in exposure between subjects with hepatic cirrhosis and normal hepatic function was predicted to be magnified during multiple dosing. The protein binding of voriconazole was not affected by impaired hepatic function.

The effect of downward dosage adjustment in chronic hepatic cirrhosis was prospectively investigated in Multiple Dose Hepatic Impairment Study (1012) The dosing regimens studied and the pharmacokinetic results in cirrhotic subjects (Child-Pugh B) and normal subjects are presented in Table 6-8.

Table 6-8 Multiple Dose Hepatic Impairment Study (1012) – Voriconazole Dose Regimens and Pharmacokinetic Parameters

	Cirrhotic Subjects (n=6)		Normal Subjects (n=6)
Loading Dose **Maintenance Dose**	**200mg q 12 h Day 1** **100mg q 12 h Days 2-6 with a single 100mg dose Day 7**		**400mg q 12 h Day 1** **200mg q 12 h Days 2-6 with a single 200mg dose Day 7**
Pharmacokinetic Results	**Cirrhotic Subjects**	**Normal Subjects**	**Ratio or difference between means (95%CI)**
C_{max} (µg/ml)	3.41	4.27	79.9% (44.8%, 142.4%)
AUCτ (µg.h/ml)	28.1	28.9	97.1% (53.6%, 176.1%)
T_{max} (h)	1.42	1.17	0.25* (-0.47, 0.97)

*For T_{max}, difference between means is used.

On the basis of these observations, the standard loading dose regimens may be used in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) but it is recommended that the maintenance dose be halved in these patients (*i.e.* dose of 100 mg bid).

The effect of chronic hepatic impairment should be distinguished from acute hepatic injury, as manifested by elevated hepatic function test results. An exploratory analysis of the relationship between baseline hepatic function test results and Week 1 mean plasma voriconazole concentrations in the therapeutic studies population showed that there was a positive association between log baseline total bilirubin and log Week 1 mean plasma concentrations. However, log baseline total bilirubin only explained 3.8% of the variability in log Week 1 mean plasma voriconazole concentrations. Baseline AST had a minor effect on Week 1 mean plasma voriconazole concentrations in addition to bilirubin while baseline ALT and alkaline phosphatase had no significant effect.

6.9.6 Renal Impairment

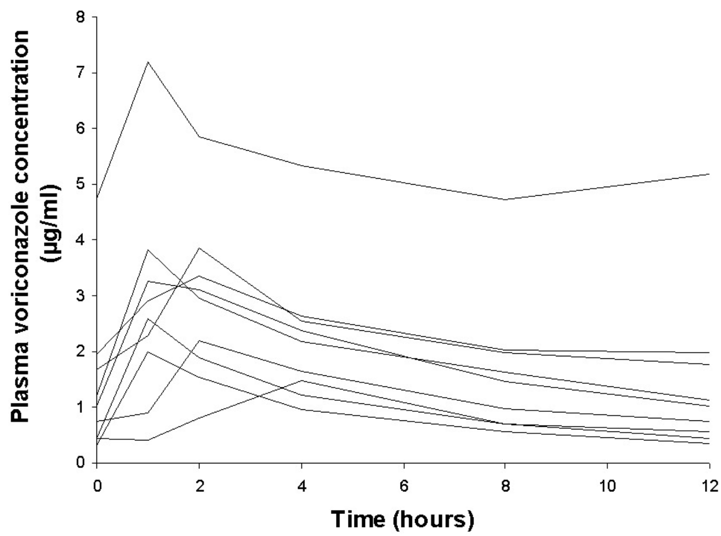
The Single Dose Renal Impairment Study (237) demonstrated that the clearance of oral voriconazole in patients with mild to severe renal impairment is not influenced by renal function. The lack of influence of renal function on the clearance of voriconazole was confirmed in the Multiple Dose Impairment Study (1016), in which intravenous voriconazole was administered to patients with moderate renal impairment. In both studies, linear regression analysis of voriconazole clearance *vs.* creatinine clearance did not show a significant association. Therefore, no dose adjustment is required for oral voriconazole in patients with renal dysfunction. However, the excipient SBECD (see "Pharmacokinetics of SBECD") in the intravenous formulation was shown to accumulate in renal impairment. Therefore, oral voriconazole should be administered to patients with moderate to severe renal impairment (serum creatinine >2.5 mg/dl) unless an assessment of the risk benefit to the patient justifies the use of intravenous voriconazole. This dosing recommendation was implemented in the Phase 3 clinical program.

The Hemodialysis Study (1011) in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with a clearance of 121 ml/min. SBECD is hemodialyzed with a clearance of 55 ml/min. Pharmacokinetic modeling showed that four-hours of hemodialysis removes 8% (CV 66%) and 46% (CV 20%) of the total body load of voriconazole and SBECD, respectively. On the basis of these findings, no dose adjustment of oral voriconazole is recommended in patients undergoing hemodialysis.

6.9.7 Adult Patients

The pharmacokinetics of voriconazole have been studied in 18 adult patients at risk of fungal infection (mainly patients with malignant neoplasms of lymphatic or hematopoietic tissue in the Multiple Dose Adult Patient Pharmacokinetic Study [673]). Patients were administered 200 mg or 300 mg of oral voriconazole q 12 h for 14 days. Individual pharmacokinetic profiles for the 200 mg q 12 h dose (n = 9) are displayed in Figure 6-8.

Figure 6-8 Multiple Dose Adult Patient Pharmacokinetic Study (673) - Individual Pharmacokinetic Profiles Following Multiple Dosing With Voriconazole 200 mg q 12 h in Patients at Risk of Fungal Infection



In this study, the observed pharmacokinetic characteristics, *i.e.* rapid and consistent absorption, gradual accumulation to steady state without the use of a loading dose regimen, and non-linear pharmacokinetics, were in agreement with those observed in healthy subjects.

6.9.8 Children

Two clinical pharmacology studies were conducted with intravenous voriconazole in children aged 2 to less than 12 years. The Single Dose Pediatric Study (249) investigated voriconazole pharmacokinetics, safety and tolerability in 11 immunocompromised children from 2 to less than 12 years of age. This was followed by the Multiple Dose Pediatric Study (1007), which investigated the pharmacokinetics, safety and toleration of voriconazole in 28 children, aged 2 to less than 12 years, who required treatment for the prevention of systemic fungal infections. A population pharmacokinetic analysis was performed using data derived from both pediatric studies. The combined dataset incorporated 355 plasma voriconazole concentrations from 35 patients. In contrast to data from adults, the pharmacokinetics of voriconazole across the studied dose range could be described by a linear pharmacokinetic model. Children had a greater elimination capacity for voriconazole than adults on a body weight basis. In common with adults, the pharmacokinetics of voriconazole are influenced by CYP2C19 genotype. After accounting for body weight, age did not significantly influence the pharmacokinetics of voriconazole in children. Pharmacokinetic simulations showed that children require a maintenance dose of 4 mg/kg IV q 12 h to achieve similar exposure produced by administration of 3 mg/kg IV q 12h in adults. Therefore, a maintenance dose of 4 mg/kg IV q 12 h is recommended for children. This was the recommended dose for patients aged two years to less than 12 years in the compassionate use studies (n=62).

6.10 Pharmacokinetics of SBECD

The excipient used to solubilize voriconazole for intravenous administration, SBECD, is pharmacologically inert and does not affect the pharmacokinetics of voriconazole. The terminal half-life of SBECD is 1.6 hours and the steady-state volume of distribution of SBECD is approximately 0.2 L/kg, which is similar to extracellular fluid volume in humans. It is renally cleared at a rate consistent with glomerular filtration rate and does not accumulate with repeated dosing over 10 days in subjects with normal renal function. The clearance of SBECD is linearly related to creatinine clearance. Accumulation of SBECD occurs in subjects with moderate to severe renal impairment (serum creatinine levels >2.5 mg/dL). It is recommended that oral voriconazole be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and if increases occur, consideration should be given to changing to oral voriconazole therapy.

6.11 Pharmacokinetics Conclusions

The pharmacokinetics of voriconazole are characterized by high oral bioavailability, large volume of distribution, cytochrome P450-mediated hepatic elimination, non-linearity, wide interindividual variability and genetic polymorphism in the CYP2C19 route of metabolism. The high oral bioavailability (96%) of voriconazole allows switching of intravenous and oral treatment and the large volume of distribution (4.6 L/kg) demonstrates extensive distribution to tissues. An extensive clinical program has provided the appropriate pharmacokinetic information to facilitate dose selection, explain the pharmacokinetic variability and provide practical guidance on dosage adjustment in special populations where clinically relevant. Dosing guidance based on the pharmacokinetics of voriconazole is provided in Sec. 9.

6.12 Drug Interactions

In vitro studies performed to characterize the metabolism of voriconazole suggested the potential for voriconazole to affect or be affected by other drugs metabolized by CYP2C19, CYP2C9 and CYP3A4. The potential for voriconazole to inhibit cytochrome P450 enzymes was studied using a series of well-established standard probe substrates in human liver microsomes (Table 6-9).

Table 6-9 Effect of Voriconazole on the Metabolism of Probe Substrates for Specific Cytochrome P450 Isozymes

Substrate	Cytochrome P450 Isozyme	Voriconazole IC_{50} μM
Phenacetin	CYP1A2	>100
Phenytoin	CYP2C9	9
S-Mephenytoin	CYP2C19	32
Bufurolol	CYP2D6	>100
Chlorzoxazone	CYP2E1	100
Felodipine	CYP3A4	50
Testosterone	CYP3A4	54
Midazolam	CYP3A4	9

Data from the *in vitro* drug metabolism studies guided an extensive Phase 1 clinical pharmacology program on drug interactions. The clinical potential for drug interactions was investigated using drugs which are likely to be co-administered to the target patient populations and/or where an interaction might be expected on mechanistic grounds. The results of drug interaction studies are summarized in Table 6-10, Table 6-11, and Table 6-12.

Table 6-10 Drug Interaction Studies Investigating the Effect of Other Drugs on the Cytochrome P450-Mediated-Metabolism of Voriconazole in Healthy Subjects

Drug & Dose	Voriconazole Dose	Study Number	Mechanism	Outcome (90% CI)	
				C_{max}	AUC
Rifampin# – 600mg QD	200 mg q 12 h;	228	P450 induction	↓93% (90%, 95%)*	↓96% (93%, 97%)*
Rifabutin – 300mg QD	200 mg q 12 h;	228	P450 induction	↓69% (57%, 77%)**	↓78% (68%, 85%)**
Rifabutin – 300mg QD	200 mg q 12 h; 400mg q 12 h (during rifabutin)	1024	P450 induction	↑104% (61%, 157%)***	↑87% (47%, 137%)***
Phenytoin## – 300mg QD	200 mg q 12 h;	233	P450 induction	↓49% (34%, 61%)*	↓69% (60%, 76%)*
Omeprazole – 40mg QD	200 mg q 12 h	247	CYP2C19 inhibition	↑15% (5%, 25%)	↑41% (29%, 55%)
Cimetidine – 400mg q 12 h	200 mg q 12 h	229	Non-specific P450 inhibition	↑18% (6%, 32%)	↑23% (13%, 33%)
Erythromycin – 1000mg q 12 h	200 mg q 12 h	243	CYP3A4 inhibition	↑ 8% (-9%, 28%)	↑ 1% (-11%, 15%)
Indinavir – 800mg tid	200 mg q 12 h	240	CYP3A4 inhibition	↑ 2% (-9%, 14%)	↑ 7% (-2%%, 18%)

*Results presented for voriconazole 200 mg q 12 h. Dose of voriconazole increased to 400mg q 12 h during co-administration with P450 inducer

** Results presented for voriconazole 200 mg q 12 h. Dose of voriconazole increased up to 350mg q 12 h during co-administration with P450 inducer

*** Results presented for voriconazole 400 mg q 12 h during rifabutin compared with voriconazole 200 mg q 12 h with placebo

#Doubling the oral dose of voriconazole from 200mg q 12 h to 400mg q 12 h during concomitant administration of rifampin only increased C_{max} and AUCτ to 34% and 19% of the pre-rifampin values, respectively

Doubling the dose of oral voriconazole from 200 mg q 12 h to 400 mg q 12 h during concomitant administration of phenytoin led to C_{max} and AUCτ values comparable to voriconazole at 200 mg q 12 h and placebo

Table 6-11 Drug Interaction Studies Investigating the Effect Of Voriconazole on Other Drugs Metabolized by Cytochrome P450 In Healthy Subjects and Patients

Drug & Dose	Voriconazole Dose	Study Number	Mechanism	Outcome (90% CI)	
				C_{max}	AUC
Omeprazole – 40mg QD	200 mg q 12 h	1013	CYP2C19 and CYP3A4 inhibition	↑116% (78%, 164%)	↑280% (228%, 341%)
Phenytoin – 300mg QD	400 mg q 12 h	241	CYP2C9 inhibition	↑ 67% (44%, 93%)	↑ 81% (56%, 110%)
Warfarin - 30mg single dose	300 mg q 12 h	239	CYP2C9 inhibition	↑8 sec (5, 12)*	↑929 sec.h (574, 1283)**
Cyclosporine# – Individualised doses in stable renal transplant recipients ranging from 75-375mg, kept constant throughout the study	200 mg q 12 h	235	CYP3A4 inhibition	↑13% (-10%, 41%)	↑70% (47%, 96%)
Tacrolimus – 0.1mg/kg single oral dose	200 mg q 12 h	1009	CYP3A4 inhibition	↑117% (86%, 152%)	↑221% (169%, 283%)
Sirolimus – 2mg single oral dose	200 mg q 12 h	1015	CYP3A4 inhibition	↑556% (473%, 652%)	↑1014% (887%, 1158%)
Rifabutin – 300mg QD	400 mg q 12 h	1024	CYP3A4 inhibition	↑ 195% (119%, 297%)	↑ 331% (247%, 436%)
Prednisolone – 60mg single dose	200 mg q 12 h	210	CYP3A4 inhibition	↑11% (-6%, 32%)	↑34% (24%, 44%)
Indinavir – 800mg tid	200 mg q 12 h	244	CYP3A4 inhibition	↓9% (-17%, 1%)	↓12% (-23%, 0%)
Tacrolimus – Individualised doses in stable hepatic transplant recipients	200 mg q 12 h	001	CYP3A4 inhibition	Study terminated after 1 subject treated with voriconazole. Trough level monitoring indicated that whole blood tacrolimus level exceeded 15ng/ml.	
Warfarin - 40mg single dose	300 mg q 12 h	234	CYP2C9 inhibition	Study terminated after first period of two-way crossover study because 4 subjects on voriconazole and warfarin and 3 subjects on placebo and warfarin had excessive increases in prothrombin time (greater than 3 times baseline)	

*Data show difference (95% CI) between means for maximum increase from baseline prothrombin time (sec)
** Data show difference (95% CI) between mean AUEC's (sec.h)
# There was a potential underestimation of the magnitude of the interaction because four subjects with excessive cyclosporine concentrations were withdrawn from the study prematurely. The trough blood cyclosporine concentrations in the subjects who discontinued the study increased by an average of 148% (range 88% to 203%).

Table 6-12 Drug Interaction Studies Investigating Non-Cytochrome P450-Mediated Mechanisms

Drug & Dose	Voriconazole Dose	Study Number.	Mechanism	Outcome (90% CI)	
				C_{max}	AUC
Effects of other drugs on voriconazole					
Azithromycin – 500 mg QD	200 mg q 12 h	243	Non-specific	↑ 8% (-9%, 28%)	↑ 1% (-11%, 15%)
Ranitidine – 150 mg q 12 h	200 mg q 12 h	229	H_2 antagonism, gastric pH increase	↑ 4% (-7%, 15%)	↑ 4% (-3%, 12%)
Effect of voriconazole on other drugs					
Mycophenolate – single oral dose of 1000 mg Mycophenolate mofetil	200 mg q 12 h	1014	Inhibition of UDP-glucuronyl transferase	↑ 2% (-9%, 15%)	↑ 10% (5%, 15%)
Digoxin 0.25 mg QD	200 mg q 12 h	236	Inhibition of P-glycoprotein transport	↑10% (-3%, 24%)	↑1% (-9%, 11%)

The results of studies investigating the effect of other drugs on the pharmacokinetics of voriconazole are summarized in Table 6-10. Voriconazole is a substrate of CYP2C19, CYP2C9, CYP3A4. Potent inducers of cytochrome P450 markedly decrease plasma voriconazole concentrations and specific recommendations are provided to increase the dose of voriconazole during concomitant administration with phenytoin or rifabutin. However, relevant specific and general inhibitors of cytochrome P450 either have a minor or no effect on voriconazole exposure.

The results of studies investigating the effect of voriconazole on the pharmacokinetics of other drugs are summarized in Table 6-11. Voriconazole inhibits three cytochrome P450 isozymes, CYP2C19, CYP2C9 and CYP3A4, with potential to increase exposure to a number of concomitant medications metabolized by these isozymes. The magnitude of interactions with CYP3A4 substrates is, however, variable ranging from no interaction (indinavir) to large increases in exposure (sirolimus). The different magnitude of the interactions across CYP3A4 substrates may be explained in part by differences in the pre-systemic metabolism of the substrates studied. However, heterogeneity in CYP3A4 interactions are increasingly recognized (Kenworthy *et al.*, 1999).

Voriconazole had no appreciable effect on the pharmacokinetics of drugs not metabolized by cytochrome P450 (see Table 6-12).

Although not studied, a number of other drug interactions are predictable from the *in vitro* and *in vivo* drug interaction data on voriconazole and other azole antifungal agents. Carbamazepine and long acting barbiturates (potent enzyme inducers) are likely to significantly decrease plasma voriconazole concentrations. Concomitant administration of voriconazole with terfenadine, astemizole, cisapride, pimozide or quinidine is contraindicated, since increased plasma concentrations of these drugs can lead to QTc prolongation and rare occurrences of *torsades de pointes.* Voriconazole may inhibit the metabolism of sulphonylureas, statins, benzodiazepines and vinca alkaloids, ergot alkaloids, non-nucleoside reverse transcriptase inhibitors (delavirdine and efavirenz) and HIV protease inhibitors other than indinavir.

The extensive clinical pharmacology program summarized above has enabled provision of practical guidance on the management of drug interactions (summarized in Table 6-13).

Table 6-13 Summary guidance on the clinical management of drug interactions

Contraindications	Dose adjustment of voriconazole	Dose adjustment and/or monitoring of other drugs	No dose adjustment of voriconazole or other drugs required
Rifampin Sirolimus Barbiturates (long acting) Carbamazepine Astemizole Cisapride Terfenadine Pimozide Quinidine Ergot alkaloids	Phenytoin[1,3] Rifabutin[1,6]	Cyclosporine[2,3] Tacrolimus[2,3] Omeprazole[2] Warfarin[4] Phenytoin[3] Sulphonylureas[5] Rifabutin[6,7] Statins[7] Benzodiazepines[7] Vinca alkaloids[7] Efavirenz[7] Nevirapine[7] HIV protease inhibitors[7] other than indinavir	Indinavir Mycophenolate mofetil Cimetidine Ranitidine Macrolide antibiotics Prednisolone Digoxin

[1]Increase intravenous maintenance dose of voriconazole to 5 mg/kg and the oral maintenance dose from 200 mg to 400 mg q 12 h. Loading dose regimen remains unchanged;
[2]Reduce dose (halve dose of cyclosporine and omeprazole, reduce dose to one third for tacrolimus)
[3]Carefully monitor blood levels
[4]Monitor prothrombin time
[5]Monitor blood glucose
[6]Monitor complete blood counts
[7]Monitor for potential drug toxicity and consider dose reduction

6.13 Overall Rationale for Guidance on Dose Adjustment based on Clinical Pharmacokinetic Data

Phase 1 studies identified chronic hepatic impairment, low body weight, CYP2C19 poor metabolizer genotype, females and the elderly as factors associated with higher exposure to voriconazole (Table 6-14). Of these, chronic hepatic impairment is likely to be the most important factor since there is potential to affect the primary clearance of voriconazole via all metabolic routes. Given clear evidence of a large effect of hepatic impairment on voriconazole exposure and the effectiveness of specific dose reduction in limiting over-exposure, dosage adjustment is recommended.

Table 6-14 Summary of factors that influence exposure to voriconazole

Dose or Administration Adjustment	Increase in Exposure	Decrease in Exposure
Adjustment recommended	Chronic hepatic impairment Low body weight (<40 kg)	Potent enzyme inducers (phenytoin, rifabutin) High fat meals (dose one hour before or one hour after meals)
No adjustment recommended	CYP2C19 poor metabolizer status Age Sex	

Voriconazole is administered intravenously on a per kg body weight basis. For practical reasons, a fixed strength of tablet is used for oral dosing. In patients less than 40 kg, the 200 mg oral dose is equivalent to doses greater than 5 mg/kg, a dose which was associated with hepatic enzyme elevations in the Multiple Dose Escalation IV/Oral Switch Study(230). Therefore, a recommendation was made to halve the oral dose to 100 mg bid in patients less than 40 kg in the Phase 3 program. This adjustment succeeded in achieving comparable plasma voriconazole concentrations in patients weighing 40 kg or more and less than 40 kg.

While CYP2C19 genotype is the most important covariate influencing the pharmacokinetics of voriconazole in healthy subjects, the population pharmacokinetic analysis showed that 69% of the interindividual variability in AUC remained unexplained after accounting for this covariate alone. Indeed, there is considerable overlap in voriconazole exposure across genotypes. Since the influence of genotype on voriconazole exposure will be confounded by drug-drug and drug-disease interactions in the patient population, no dose adjustment based on genotype is recommended. The population pharmacokinetic analysis showed that gender and age have a weaker influence on voriconazole exposure than CYP2C19 genotype. Along with evidence that these factors do not affect the safety profile of voriconazole in therapeutic studies, no dose adjustment is recommended in females and the elderly.

Phase 1 studies also identified concomitant administration with enzyme inducers and high fat meals as factors which reduce exposure to voriconazole (Table 6-14). The enzyme inducing effects of phenytoin and rifabutin may be overcome by administration of doubled oral doses of voriconazole. This was implemented in the Phase 3 program. Although the effect of food on voriconazole exposure is relatively small, it was consistently seen, and so a recommendation to administer oral voriconazole at least one hour before or one hour following a meal was implemented in the Phase 3 program. This recommendation is made to minimize the risk of inadequate exposure in patients treated for serious fungal infections.

6.14 Dose Selection for Therapeutic Studies

6.14.1 Nonclinical and Clinical Pharmacokinetic Data

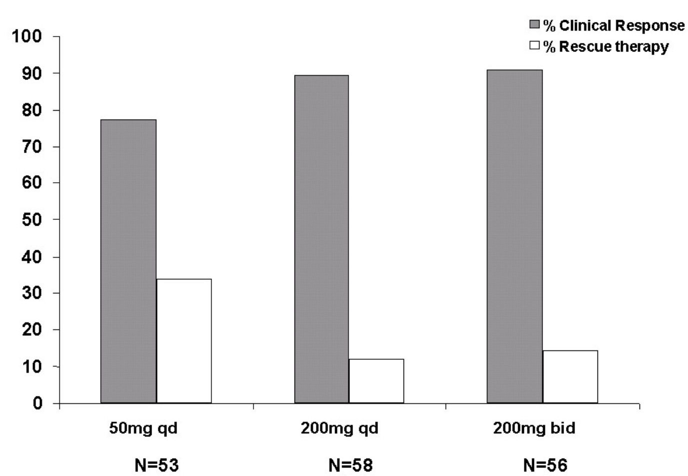
Dose selection for voriconazole was based initially on MIC data from pre-clinical studies and pharmacokinetic data from the Phase 1 program. These data were used to suggest doses in man which would achieve unbound plasma voriconazole concentrations above the MIC for the majority of clinically relevant fungal pathogens. For Aspergillosis, a total plasma voriconazole concentration of greater 1 μg/ml (unbound voriconazole concentration of 0.42

µg/ml) was targeted to exceed the MIC for *Aspergillus* spp.(range 0.19 to 0.50 µg/ml for stock isolates). The Phase 1 pharmacokinetic data showed that intravenous doses of 3 to 4 mg/kg q 12 h and oral doses of 200 to 300 mg q 12 h would allow the attainment of plasma concentrations above 1 µg/ml for some period of the dose interval in the majority of subjects. Characterization of the pharmacokinetics of voriconazole in Phase 1 also allowed the design of a loading dose regimen for rapid attainment of steady state, switching from intravenous to oral administration, and appropriate dose escalation with due consideration of the non-linearity in pharmacokinetics.

6.14.2 Dose Ranging Study in Oropharyngeal Candidiasis

The Dose Ranging Oropharyngeal Candidiasis Study (302) was a randomized, double-blind, dose-ranging study using oral dose regimens of 50mg once daily, 200mg once daily, or 200mg bid for seven days to assess the comparative efficacy of voriconazole in the treatment of oropharyngeal candidiasis in HIV-infected patients. The dose of 50 mg once daily was associated with a lower clinical response and higher proportion of subjects requiring rescue therapy compared with either 200 mg once daily or 200 mg bid (Figure 6-9). (Troke, *et. al.*, 1995)

Figure 6-9 Dose Ranging Oropharyngeal Candidiasis Study (302) - Relationship Between Dose and Clinical Response or Requirement for Rescue Therapy



The majority of pre-dose trough plasma voriconazole concentrations from the 200 mg q 12 h regimen exceeded the mean MIC for *Candida albicans* (0.05 µg/ml; stock isolates) by greater than 10 fold (Table 6-15).

Table 6-15 Dose Ranging Oropharyngeal Candidiasis Study (302) - Relationship Between Dose and Trough Plasma Voriconazole Concentrations

Voriconazole Dose	Number of Subjects with trough plasma voriconazole concentrations greater than 0.5 µg/ml (n/N)
50 mg QD	0/9
200 mg QD	3/12
200 mg q 12 h	10/14

The 200 mg once daily regimen was rejected on the basis of wider peak to trough fluctuation in plasma voriconazole concentrations and low trough plasma voriconazole concentrations compared with a 200 mg bid regimen. Since acceptable safety profile was also observed, the 200mg bid regimen was chosen for further studies.

6.14.3 Maximum Tolerated Dose

Since serious fungal infections are potentially life-threatening, dose regimens should be designed to deliver maximal exposure to voriconazole commensurate with acceptable tolerability. The maximum tolerated dose regimen was identified in the Multiple Dose Escalation IV/Oral Switch Study (230) which was a parallel group, double blind, randomized, placebo-controlled study to investigate the safety, tolerability and pharmacokinetics of voriconazole when administered as an intravenous loading dose (6mg/kg q 12 h for 2 doses) followed by six days maintenance intravenous doses (3mg/kg, 4mg/kg or 5mg/kg q 12 h) followed by 6.5 days oral dosing (200mg q 12 h, 300mg q 12 h or 400mg q 12 h). Elevation of liver enzymes was the dose limiting factor in this study. Table 6-16 summarizes the number of subjects with transaminase elevations (above the upper limit of normal which were 72 and 59 IU/L for ALT and AST, respectively, for the laboratory used in this study) by dose of voriconazole.

Table 6-16 Multiple Dose Escalation IV/Oral Switch Study (230) – Alanine Transaminase (ALT)/Aspartate Transaminase (AST) Elevations by Dose of Voriconazole

Voriconazole Dose	Number of Subjects with ALT/AST elevations (n/N)
(6+3)mg/kg IV to 200 mg oral q 12 h	0/14
(6+4)mg/kg IV to 300 mg oral q 12 h	1/7
(6+5)mg/kg IV to 400 mg oral q 12 h	5/14

ALT = alanine transaminase; AST = aspartate transaminase

Voriconazole at 5 mg/kg q 12h IV, followed by 400 mg q 12 h orally, was associated with ALT and AST elevations in 5 of 14 subjects. Therefore, a maintenance dose of 4mg/kg q 12h IV followed by 300mg bid orally represents the maximum tolerated multiple dose regimen of voriconazole.

7 EFFICACY

This briefing document focuses on the efficacy of voriconazole in the primary treatment of invasive aspergillosis and in empirical therapy in patients with persistent fever and neutropenia demonstrated in clinical trials. Supportive data on the treatment of voriconazole in esophageal candidiasis are also presented in Section 7.4.1. Additional data supporting the efficacy in the treatment of invasive aspergillosis, nonesophageal candidiasis (referred to as systemic candidiasis), and infections due to emerging pathogens are provided in Appendices 3 and 4. Details of the studies included in this efficacy section are summarized in Appendix 2.

7.1 Aspergillosis

The efficacy of voriconazole in the treatment of infections caused by *Aspergillus* species is established by the findings of the randomized open label Global Comparative Aspergillosis Study (307/602) as well as the supportive Non-Comparative Aspergillosis Study (304) and the contemporaneous Historical Control Study (1003).

7.1.1 Global Comparative Aspergillosis Study (307/602)

Two randomized, comparative, open label, Phase 3 studies of voriconazole in the primary treatment of acute invasive aspergillosis were initiated in 1997: Study 307, led by the European Organization for Research and Treatment of Cancer (EORTC) and Study 602, led by U.S. investigators. Studies 307 and 602 had identical entry criteria, treatment regimens, study procedures, and outcome assessments and were run in parallel; they were conducted from July 1997 to February 2001 and September 1997 to January 2001, respectively. They included a total of 199 centers and 392 patients; the studies were conducted in U.S., Europe, Israel, Canada, Australia, Brazil, Argentina, Colombia, Mexico, and India.

A proposal to conduct a combined analysis of interim data from Studies 307 and 602 was discussed with FDA in 1996. The statistical analysis plan to analyze the first 276 evaluable patients was first drafted in 1997, referred to as the umbrella analysis. In October 2000, a consensus recommendation was made by the EORTC, the U.S. investigative group and the Sponsor to close enrollment. Reasons for this recommendation were reduced use of the comparative agent used in the trials, standard amphotericin B, and consequent difficulties in enrollment of patients and new sites. The decision to terminate enrollment was made prior to any analysis of efficacy data. This decision was shared with FDA. At that time, 392 patients were enrolled. The data were analyzed according to the umbrella analysis plan and are presented here as the Global Comparative Aspergillosis Study (307/602). This analysis includes all patients recruited and treated in these two studies.

7.1.1.1 Study Objectives

The protocol-specified objectives of the individual studies were similar: to compare the efficacy, safety and tolerability of voriconazole *vs.* conventional amphotericin B (both of which could be followed by Other Licensed Antifungal Therapy, as appropriate) in the treatment of acute invasive aspergillosis in immunocompromised patients. In Study 307, an additional objective was to compare the survival and resource utilization in patients treated with voriconazole *vs.* conventional amphotericin B with or without Other Licensed Antifungal Therapy.

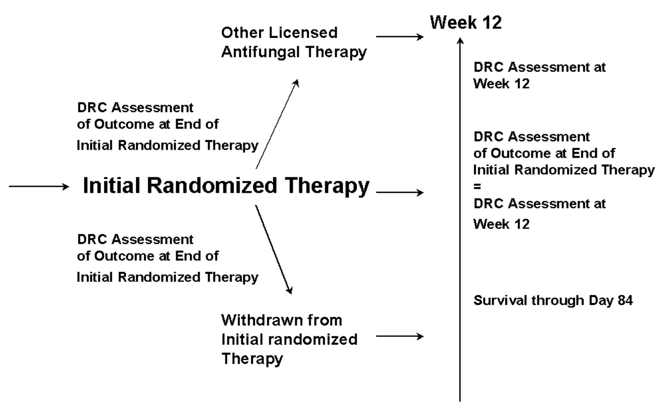
The primary objective of the umbrella analysis, the Global Comparative Aspergillosis Study (307/602), was to compare the efficacy of voriconazole *vs.* amphotericin B (both of which could be followed by Other Licensed Antifungal Therapy, as appropriate) for the treatment of acute invasive aspergillosis in immunocompromised patients.

7.1.1.2 Study Design

Studies 307 and 602 were open label, randomized, comparative studies of voriconazole (followed by Other Licensed Antifungal Therapy) *vs.* amphotericin B (followed by Other Licensed Antifungal Therapy) in immunocompromised patients with acute invasive aspergillosis. The two protocols had identical entry criteria, treatment regimens, study procedures, and outcome assessments.

The study procedures are illustrated in Figure 7-1.

Figure 7-1 Global Comparative Aspergillosis Study (307/602) - Study Procedures



Eligible patients were randomized at study entry to receive initial study treatment (initial randomized treatment, IRT) with either voriconazole or amphotericin B deoxycholate (conventional amphotericin B). Voriconazole was administered with two loading doses of 6mg/kg IV q 12 h x 2 doses, then 4mg/kg q 12 h for at least seven days (minimum 3 mg/kg q 12 h), then oral voriconazole 200 mg bid up to a total of 12 weeks (patients weighing less than 40 kg received 100 mg bid). The dose could be increased to 300 mg bid (150 mg bid in patients weighing less than 40 kg) if the patient was not improving after at least three days of therapy. Dose adjustments of voriconazole were allowed based on tolerability and clinical response. The maximum and minimum intravenous doses of voriconazole were 6 mg/kg q 12 h and 3mg/kg q 12 h, respectively. The maximum and minimum oral doses of voriconazole were 300 mg bid (150 mg bid for patients <40 kg) and 200 mg bid (100 mg bid for patients <40 kg), respectively.

Amphotericin B was administered at a dose of 1.0-1.5 mg/kg/day (0.75 mg/kg/day for patients treated with concomitant cyclosporine and tacrolimus) as a slow IV infusion to be maintained for two weeks and could be continued for a maximum of 12 weeks. The dose of amphotericin B could be adjusted based upon toxicity, intolerance, or clinical failure. The investigators were instructed that initial therapy with amphotericin B was to continue for at least 14 days.

In both arms, patients were allowed to switch to Other Licensed Antifungal Therapy if they failed to respond or were unable to tolerate initial randomized therapy. Other Licensed Antifungal Therapy was defined as any commercially-available therapy approved for use in the treatment of aspergillosis, or any unapproved antifungal agent available by compassionate use. Patients could be treated with amphotericin B as Other Licensed Antifungal Therapy but not voriconazole. Patients who were switched to Other Licensed Antifungal Therapy could continue on this therapy for the remainder of the study.

Patients could be treated for a maximum of 12 weeks and were monitored in the study for 16 weeks. They were to be followed for the entire 16 week study period, regardless of any changes in treatment. Clinical, radiological, mycological, and global responses (incorporating clinical and radiological responses) were assessed by the investigator at Weeks 6 and 12, end of randomized therapy, and Week 16. Clinical, radiological and mycological evaluations were performed separately by both the investigator who enrolled the patient and by a single-blinded Data Review Committee composed of antifungal experts and radiologists.

The global response was categorized as one of five possible outcomes: complete, partial, stable, failure, or indeterminate. An outcome of success was assigned for patients with complete and partial response; all other patients were assessed as failures. Mycological response was also assessed.

Two independent Data Safety Monitoring Boards (DSMBs) reviewed interim safety data at pre-specified time points. For Study 602, safety reports summarizing deaths and serious adverse events (SAEs) were submitted to the Chair of the DSMB quarterly or after each 20 deaths, whichever was sooner. For Study 307, the EORTC established its DSMB, that initially reviewed the safety after the first 50 deaths.

7.1.1.3 Key Entry Criteria

Patients with a diagnosis of definite or probable acute invasive aspergillosis, based on definitions developed by the European Organization for the Research and Treatment of Cancer (EORTC) and the National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group (MSG), with at least one of the following immunosuppressive conditions: allogeneic or autologous bone marrow/peripheral stem cell transplant; hematological malignancy (including lymphoma); aplastic anemia and myelodysplastic syndrome; solid organ transplantation; solid organ malignancy (after cytotoxic chemotherapy); human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS); or treatment with prolonged high dose corticosteroid or other immunosuppressive therapy. The fungal infection at baseline was to be newly diagnosed, and only up to 96 hours of prior systemic antifungal therapy was allowed. Important exclusion criteria included: alanine transaminase, aspartate transaminase, or alkaline phosphatase above five times the upper limit of normal, serum creatinine >2.5 mg/dL, life expectancy less than 72 hours, and administration of excluded concomitant medications.

7.1.1.4 Statistical Methods

Efficacy Endpoints and Analyses

The two protocols had identical endpoints, only the assignment of primary versus secondary endpoint differed. Table 7-1 shows the primary and secondary endpoints for each study and for the umbrella analysis.

Table 7-1 Global Comparative Aspergillosis Study (307/602) - Primary and Secondary Efficacy Endpoints by Study

Endpoint	Umbrella Analysis	Study 602	Study 307
Outcome at Week 12 (Test for non-inferiority)	Primary	Primary	Secondary
Outcome at End of Randomized Therapy (Test for superiority)	Secondary	Secondary	Primary
Survival through Day 84	Secondary	Secondary	Secondary

Primary Endpoints

Efficacy assessments were performed by the Data Review Committee.

The primary end point was success (satisfactory global response) at Week 12 as assessed by the Data Review Committee (DRC). Success was defined as complete [cure] or partial [improvement] response. The primary efficacy analysis (stratified by protocol) compared success rates between treatment arms at Week 12 in the Modified Intention to Treat population. The prospectively defined analysis of the primary endpoint entailed the construction of a stratified 95% confidence interval for the difference in the success rate between treatments in the Modified Intention to Treat population. The confidence interval was derived from a method of linear stratification that weighted according to the reciprocal of the variance. The analysis included the protocol term. The confidence interval was compared with a non-inferiority margin of –20%. An unstratified analysis was also performed.

Secondary Endpoints

Secondary endpoints were defined in the umbrella protocol and statistical analysis plan as success at end of initial randomized treatment as assessed by the Data Review Committee and survival through Day 84 from the start of treatment between treatment groups in the Modified Intention to Treat population.

The secondary efficacy analyses were to demonstrate superiority of voriconazole at end of randomized treatment in the Modified Intention to Treat population and to assess survival through Day 84 (from the start of treatment) between treatment groups in that same population. Time to discontinuation of Initial Randomized Therapy was also assessed.

Voriconazole was to be considered superior to amphotericin B if the lower limit of the 95% confidence interval for the difference in the success rate in the two groups did not include 0 and was >0%. For the survival type secondary endpoints, the treatment effect (hazard ratio and 95% confidence interval) was estimated from a Cox proportional-hazards model stratified by protocol and cumulative survival Kaplan-Meier curves were constructed. The results of the survival analysis were not adjusted for interim safety analyses performed by the Data Safety Monitoring Boards.

The secondary analyses were also performed on the Intention to Treat and Per Protocol populations.

Analysis Populations

The primary analysis population was a Modified Intention to Treat population. In order to address the guidance given in International Conference on Harmonization (ICH) E-9 concerning appropriate analysis populations for non-inferiority trials, the primary analysis was performed on the Per Protocol population to explore the robustness of the results of the primary analysis. The primary analysis was also performed on the Intention to Treat population.

The definitions of the analysis populations are summarized in Table 7-2.

Table 7-2 Global Comparative Aspergillosis Study (307/602) – Analysis Populations

Population	Criteria
Intention to Treat	• All patients who received at least one dose of their initial randomized treatment
Modified Intention to Treat	• All patients who received at least one dose of their initial randomized therapy • Had Data Review Committee confirmed definite or probable diagnosis of invasive aspergillosis at baseline
Per Protocol	• All patients who received at least one dose of their initial randomized therapy • Had Data Review Committee confirmed definite or probable diagnosis of invasive aspergillosis at baseline • Did not have a Data Review Committee-assessed exclusion o for receiving prohibited concomitant medication o for other eligibility/evaluability reasons • Did not have an indeterminate response as assessed by the Data Review Committee • Did not receive concomitant treatment with Other Licensed Antifungal Therapy during the first three days of initial randomized therapy

Sample Size Determination

The sample size of the umbrella analysis of the Global Comparative Aspergillosis Study (307/602) was based on the following: a non-inferiority criterion which required that the lower bound of the 95% confidence interval of the difference in success rates was greater than -20%; a superiority criterion which required that 95% confidence interval for the difference in the success rate in the two groups did not include 0 and the lower bound of the 95% confidence interval was > 0% and an alternative hypothesis of a difference of 20% in the response rates between treatments; an expected overall success rate of 50% in both treatment groups; a power of at least 90% to achieve both efficacy objectives; an expected 75% of the patients enrolled would have a confirmed baseline diagnosis of probable or definite aspergillosis by the Data Review Committee. Thus 264 evaluable Modified Intention to Treat patients were required for the Week 12 non-inferiority analysis (primary) and 276 Modified Intention to Treat patients for the end of randomized treatment superiority analysis (secondary). Therefore, assuming 25% of randomized patients would be excluded from the Modified Intention to Treat analysis, 368 patients were needed to provide the required 276 patients in the Modified Intention to Treat population.

Randomization and Stratification

Patients were randomized into the two studies using a minimization algorithm, which included center and the pre-specified stratification factors (site of infection, underlying diagnosis, and neutrophil count) (Table 7-3).

Table 7-3 Global Comparative Aspergillosis Study (307/602) - Stratification Factors

Stratification Variables	Details
Protocol	Study 307 *vs.* Study 602
Site of infection	Pulmonary *alone vs.* Extra-Pulmonary
Underlying disease	• Allogeneic BMT/PSCT, *vs.* • Autologous BMT/PSCT OR other hematological condition (*e.g.*, leukemia) *vs.* • Other immunocompromised state (*e.g.*, solid organ transplant, HIV/AIDS)
Neutrophil count	ANC< 500 cells/mm^3 *vs.* ≥ 500 cells/mm^3

AIDS = acquired immunodeficiency syndrome; ANC = absolute neutrophil count; BMT = bone marrow transplant; HIV = human immunodeficiency virus; PSCT = peripheral stem cell transplant;

Statistical Analysis Plan

The first draft of the statistical analysis plan for the umbrella analysis was produced on 2 June 1997 and was finalized 29 January 1998 after discussions with the FDA. The statistical analysis plan was subsequently updated for reporting purposes on 22 December 2000, prior to database release to reflect the decision to close the individual studies.

Changes from the pre-specified analyses in the statistical analysis plan:

The statistical analysis plan stated that the primary and secondary efficacy analyses would be performed using a stratified analysis. The covariates to be used in the stratified analysis were to be protocol (Study 307 *vs.* Study 602), neutrophil status, site of diagnosis and underlying disease. However, examination of the contingency table for the combination of the stratification factors showed that more than half of the entries had counts of 10 or less, including one with zero. Fitting the statistical models as specified would have resulted in instability, inefficiency and poor fit. Instead, only the protocol term was included as a covariate in the primary analysis. Additional analyses were then performed including protocol (Study 307 *vs.* Study 602) and each of the other covariates separately, to examine any effects of including additional stratification variables.

Protocol Amendments affecting the statistical analysis included:

1. Clarification of the role of the Data Safety Monitoring Boards and description of the use of the Data Review Committee assessments in the statistical analyses. Modified Intention to Treat population will be based upon the Data Review Committee assessment of baseline diagnosis. Data Review Committee assessments of global response will be used in the efficacy analyses.

2. Announcement of closure of each study and the intention to replace the separate study analyses with a combined statistical analysis. Because the decision to terminate enrollment was made without knowledge of the efficacy results, this analysis is treated as

the final analysis and, therefore, no statistical adjustment for early termination is necessary.

Interim Analyses

External Data Safety Monitoring Boards for each study performed interim assessments to oversee the progress of the study and to ensure that enrolled patients were not exposed to unacceptable toxicity. As part of this assessment, interim analyses of mortality were performed. No interim analyses of efficacy were performed for either study. Results from the interim analysis of mortality were not shared with the sponsor.

As per the Study 307 Data Safety Monitoring Board agreement, the Data Safety Monitoring Board met after 50 deaths had been observed on the study. At this interim analysis, 132 patients were randomized into the study. The Data Safety Monitoring Board members concluded after their closed session meeting that there were no safety related reasons preventing continuation of Study 307 and the Data Safety Monitoring Board did not consider meeting again.

The Study 602 Data Safety Monitoring Board met twice during the course of the study. For the first interim analysis, 83 patients randomized into the study were assessed, of whom 38 had died. The Data Safety Monitoring Board recommended that the study continue to accrue and follow patients as originally planned in the study.

For the second interim analysis, 124 randomized patients were assessed, of whom 63 had died. The Data Safety Monitoring Board concluded after their closed session meeting that there were no safety related concerns but agreed with the sponsor's proposal to close recruitment into the study due to change in the medical practice and slow recruitment. All ongoing patients were followed up as planned in the study.

An administrative analysis of the combined safety data was performed on data with a cut-off date of 20 September 1999 for inclusion in the integrated safety summaries as part of the New Drug Application.

7.1.1.5 Data Review Committee

A Data Review Committee performed an independent review of the data generated from the two studies. The Data Review Committee had two subgroups. The members of the European subgroup were elected by the EORTC and the members of the U.S. subgroup were selected by the Sponsor. The Data Review Committee was composed of a group of 12 physicians. These physicians included American and European infectious disease specialists, hematologist-oncologists and radiologists. A global standard operating procedure was developed and followed at all Data Review Committee meetings. The Data Review Committee determined the certainty of diagnosis of acute invasive aspergillosis, assessed the global response to therapy at end of randomized therapy and Week 12, and the cause of death (if applicable) in a blinded fashion. In assessing global response, the Data Review Committee used all available clinical, radiological (including digitized X-rays and CT scans) and histopathological and mycological data, as well as investigator assessments. The DRC procedures required that a number of cases be exchanged between subgroups to evaluate consistency of Data Review Committee assessments. Initially, 40 patients were reviewed for diagnostic certainty and 36 were assessed by both DRC subgroups as meeting criteria for definite or probable invasive aspergillosis (Patterson, *et. al.*, 2000). For 37 patients, response was assessed by both DRC subgroups and agreement on outcome occurred for 92% of these patients (Denning et. al., 2000). An additional 46 patients were reviewed for diagnostic certainty and outcome by both subgroups. In all reviewed cases, differences in key efficacy variables (including response and certainty of diagnosis) were resolved by consensus.

7.1.1.6 Protocol Amendments

Protocol amendments to both protocols implemented after study initiation that affected entry criteria, efficacy or safety assessments included the following:

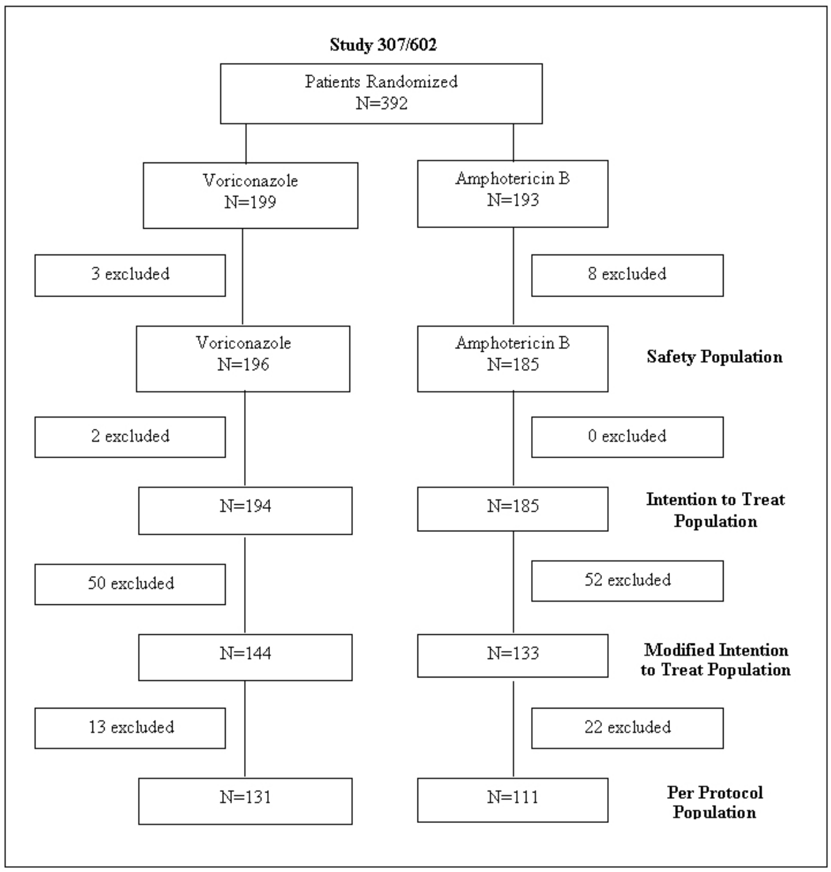
1. Clarification of the definition of definite aspergillosis (removed biopsy/culture of a nasal lesion from the inclusion criteria pertaining to the isolation of the *Aspergillus* species).
2. Updated guidance on concomitant medications:
    - Changed exclusion criteria from greater than three days of rifampin, rifabutin, and/or carbamazepine within the 14 days prior to study entry, to receipt of these concomitant medications at anytime within the 14 days prior to study entry.
    - Added exclusion for patients who were receiving and could not discontinue the following drugs at least 24 hours prior to randomization: terfenadine, cisapride astemizole, or sulphonylureas.
    - Added prohibition of systemic antifungal agents, including itraconazole, fluconazole, or amphotericin B preparations which must have been discontinued before enrollment. Coadministration of any systemic antifungal agent with voriconazole during the study was prohibited.
    - Added information about concomitant medications that were not contraindicated, but could interact with voriconazole.
3. Removal of the upper limit on the duration of IV voriconazole therapy.
4. Clarification of the role of the Data Safety Monitoring Boards (DSMBs) and description of the use of the Data Review Committee assessments in the statistical analyses.
    - Data Review Committee confirmation of the baseline diagnosis and assessment of the global response at Weeks 6 and 12 and at End of Therapy for all patients and the identification of a Modified Intention to Treat population based upon Data Review Committee assessment of baseline diagnosis.
5. Addition of requirement for cardiac monitoring for patients at risk of arrhythmia.
6. Addition of requirement for correction of hypokalemia prior to voriconazole infusion in affected patients.
7. Addition of prohibition of the simultaneous infusion of study treatment with blood products or electrolytes.
8. Announcement of closure of each study and the intention to replace the separate study analyses with a combined statistical analysis.

7.1.1.7 Results

Patient Disposition

The evaluation groups of enrolled patients are summarized in Figure 7-2.

Figure 7-2 Global Comparative Aspergillosis Study (307/602) – Evaluation Groups



The reasons for exclusion from the Safety, Intention to Treat, Modified Intention to Treat and Per Protocol analyses and the numbers of patients excluded from each arm of the study are shown in Table 7-4.

Table 7-4 Global Comparative Aspergillosis Study (307/602) - Reasons for Exclusion from Analysis Populations – Safety, Intention to Treat, Modified Intention to Treat, and Per Protocol Populations

Analysis Population **Reason for Exclusion**	**Voriconazole Randomized (N=199) Number excluded from population**	**Amphotericin B Randomized (N=193) Number excluded from population**
Safety Population		
Received no medication	3	8
Intention to Treat		
Improperly randomized	2	0
Modified Intention to Treat		
No definite/probable diagnosis as assessed by the Data Review Committee	50	52
Per Protocol*		
Eligibility or evaluability ticked no by the Data Review Committee on the patient evaluation form**	9	16
Received excluded concomitant medication	2	4
Indeterminate global response at Week 12	5	5
Took IRT and OLAT simultaneously for 3 or more consecutive days at baseline	0	2
Total	13	22

IRT=initial randomized treatment; OLAT=Other Licensed Antifungal Therapy
*Patients can be excluded for more than one reason.
**Reasons include > 96 hours of prior antifungal therapy (n=7), infections with pathogens other than *Aspergillus* (n=6), liver function tests > five times upper limit of normal (n=4), miscellaneous [chronic invasive aspergillosis, insufficient steroid dose, no underlying immunocompromising condition]; patients were excluded for more than one reason.

Disposition of all treated patients (Intention to Treat and Modified Intention to Treat populations) is summarized in Table 7-5.

Table 7-5 Global Comparative Aspergillosis Study (307/602) - Patient Disposition – Intention to Treat and Modified Intention to Treat Populations

	Intention to Treat		Modified Intention to Treat	
	Voriconazole (N=194) n	**Amphotericin B (N=185) n**	**Voriconazole (N=144) n**	**Amphotericin B (N=133) n**
Completed the study on randomized Therapy	79	7	56	3
Completed <12 weeks of therapy	10	7	7	3
Completed on day 84 or received ≥12 weeks of therapy	69	0	49	0
Withdrew while on randomized therapy	41	34	36	23
Switched to Other Licensed Antifungal Therapy	74	144	52	107
Total	194	185	144	133

In both the Intention to Treat and the Modified Intention to Treat populations, more voriconazole than amphotericin B patients completed the study on initial randomized therapy.

Baseline Characteristics/Demographics

The demographic characteristics of voriconazole and amphotericin B-treated patients in the Intention to Treat and Modified Intention to Treat populations were similar, and are presented in Table 7-6 and Table 7-7.

Table 7-6 Global Comparative Aspergillosis Study (307/602) – Demographic Characteristics - Intention to Treat Population

	Voriconazole (N=194)			Amphotericin B (N=185)		
	Males (N = 127)	**Females (N = 67)**	**Total (N = 194)**	**Males (N = 114)**	**Females (N = 71)**	**Total (N = 185)**
Age range (years)	13 –77	20 – 79	13 – 79	15 – 75	12 – 74	12 – 75
Mean	48.4	49.3	48.7	50.4	51.0	50.6
Weight range (kg)	39.0-135.9	42.3–119.5	39.0-135.9	40.0-117.9	28.0-100.3	28.0-117.9
Mean	73.2	66.4	70.9	73.2	65.9	70.4
Race n (%)						
White	114 (89.8)	60 (89.6)	174 (89.7)	107 (93.9)	68 (95.8)	175 (94.6)
Black	5 (3.9)	3 (4.5)	8 (4.1)	0 (0)	2 (2.8)	2 (1.1)
Asian	4 (3.1)	2 (3.0)	6 (3.1)	2 (1.8)	0 (0)	2 (1.1)
Other	4 (3.1)	2 (3.0)	6 (3.1)	5 (4.4)	1 (1.4)	6 (3.2)

Table 7-7 Global Comparative Aspergillosis Study (307/602) – Demographic Characteristics – Modified Intention to Treat Population

	Voriconazole N = 144			Amphotericin B N = 133		
	Males (N = 98)	**Females (N = 46)**	**Total (N = 144)**	**Males (N = 89)**	**Females (N = 44)**	**Total (N = 133)**
Age range (years)	13 – 77	20 – 79	13 – 79	15 –75	12 – 72	12 – 75
Mean	48.9	47.7	48.5	50.4	50.6	50.5
Weight range (kg)	39.0-123.0	42.3-119.5	39.0-123.0	40.0-117.9	28.0-95.7	28.0-117.9
Mean	72.0	66.9	70.4	73.5	66.0	71.0
Race n (%)						
White	88 (89.8)	42 (91.3)	130 (90.3)	84 (94.4)	42 (95.5)	126 (94.7)
Black	5 (5.1)	2 (4.3)	7 (4.9)	0 (0)	1 (2.3)	1 (0.8)
Asian	3 (3.1)	1 (2.2)	4 (2.8)	0 (0)	0 (0)	0 (0)
Other	2 (2.0)	1 (2.2)	3 (2.1)	5 (5.6)	1 (2.3)	6 (4.5)

All randomized patients had an investigator assessed primary diagnosis of acute invasive aspergillosis.

Table 7-8 provides a summary of site of infection, underlying disease and neutrophil count for the Intention to Treat and Modified Intention to Treat populations at baseline.

Table 7-8 Global Comparative Aspergillosis Study (307/602) – Data Review Committee-Assessed Site of Infection, Data Review Committee-Assessed Underlying Disease and Neutrophil Status at Baseline – Intention to Treat and Modified Intention to Treat Populations

	Intention to Treat		Modified Intention to Treat	
	Voriconazole N = 194 n (%)	**Amphotericin B N = 185 n (%)**	**Voriconazole N = 144 n (%)**	**Amphotericin B N = 133 n (%)**
Site of Infection*				
Pulmonary	119 (61.3)	112 (60.5)	119 (82.6)	112 (84.2)
Extrapulmonary	25 (12.9)	21 (11.4)	25 (17.4)	21 (15.8)
Other**	50 (25.8)	52 (28.1)	0	0
Underlying Disease*				
Allogeneic BMT/PSCT	44 (22.7)	38 (20.5)	37 (25.7)	30 (22.5)
Autologous BMT/PSCT or hematological condition (e.g., leukemia)	118 (60.8)	120 (64.9)	81 (56.3)	84 (63.2)
Autologous BMT/PSCT	12 (6.2)	8 (4.3)	6 (4.2)	6 (4.5)
Hematological condition (e.g., leukemia)	106 (54.6)	112 (60.5)	75 (52.1)	78 (58.6)
Other immunocompromised state	32 (16.5)	27 (14.6)	26 (18.0)	19 (14.3)
HIV/AIDS	6 (3.1)	7 (3.8)	6 (4.2)	7 (5.3)
Solid organ transplantation	11 (5.7)	8 (4.3)	9 (6.3)	5 (3.8)
Solid organ malignancy	1 (0.5)	0	1 (0.7)	0
High dose corticosteroid therapy	11 (5.7)	12 (6.5)	9 (6.3)	7 (5.3)
Other	3 (1.5)	0	1 (0.7)	0
Neutrophil Status				
ANC <500 cells/mm^3	92 (47.4)	84 (45.4)	63 (43.8)	60 (45.1)
ANC $\geq$500 cells/mm^3	102 (52.6)	101 (54.6)	81 (56.3)	73 (54.9)

AIDS = acquired immunodeficiency syndrome; ANC = absolute neutrophil count; HIV = human immunodeficiency virus
*Data Review Committee assessment
**Other includes infections that did not meet the protocol specified criteria according to the Data Review Committee

Underlying disease and neutrophil count were similar for patients in the two treatment arms. The sites of infection were similar between treatment groups. According to the Data Review Committee, most patients in both the voriconazole arm and the amphotericin B arm had pulmonary aspergillosis.

The certainty of infections at baseline, as assessed by the Data Review Committee, in the entire study population and by study in the Intention to Treat and Modified Intention to Treat populations are presented in Table 7-9 and Table 7-10.

Table 7-9 Global Comparative Aspergillosis Study (307/602) – Data Review Committee-Assessed Certainty of Infection in Entire Population – Intention to Treat and Modified Intention to Treat Populations

Analysis Population	Certainty of Infection	Voriconazole n (%)	Amphotericin B n (%)
ITT	Definite	67 (34.5)	41 (22.2)
	Probable	77 (39.7)	92 (49.7)
	Other*	50 (25.8)	52 (28.1)
	Total	194 (100.0)	185 (100.0)
MITT	Definite	67 (46.5)	41 (30.8)
	Probable	77 (53.5)	92 (69.2)
	Total	144 (100.0)	133 (100.0)

ITT = Intention to Treat; MITT = Modified Intention to Treat
*Other = includes infections that are not aspergillosis and those that did not meet the protocol specified criteria according to the Data Review Committee.

Table 7-10 Global Comparative Aspergillosis Study (307/602) – Data Review Committee Assessed Certainty of Infection by Study – Intention to Treat and Modified Intention to Treat Populations

Analysis Population	Certainty of Infection	Voriconazole		Amphotericin B	
		Study 602 n (%)	Study 307 n (%)	Study 602 n (%)	Study 307 n (%)
ITT	Definite	30 (44.1)	37 (29.4)	21 (32.8)	20 (16.5)
	Probable	28 (41.2)	49 (38.9)	28 (43.8)	64 (52.9)
	Other*	10 (14.7)	40 (31.7)	15 (23.4)	37 (30.6)
	Total	68 (100.0)	126 (100.0)	64 (100.0)	121 (100.0)
MITT	Definite	30 (51.7)	37 (43.0)	21 (42.9)	20 (23.8)
	Probable	28 (48.3)	49 (57.0)	28 (57.1)	64 (76.2)
	Total	58 (100.0)	86 (100.0)	49 (100.0)	84 (100.0)

ITT = Intention to Treat; MITT = Modified Intention to Treat
*Other = includes infections that are not aspergillosis and those that did not meet the protocol specified criteria according to the Data Review Committee.

In both the Intention to Treat and the Modified Intention to Treat populations, there were more patients with definite infections in the voriconazole treatment group than in the amphotericin B treatment group (34.5% *vs.* 22.2% in the Intention to Treat population and 46.5% *vs.* 30.8% in the Modified Intention to Treat population). Within each treatment group, there were proportionally more definite infections in the primarily U.S.-based Study 602 than in the primarily Europe-based Study 307.

Treatment

Table 7-11 and Table 7-12 show the number of patients on initial randomized therapy or Other Licensed Antifungal Therapy on Day 84 in the Intention to Treat and Modified Intention to Treat populations, respectively.

Table 7-11 Global Comparative Aspergillosis Study (307/602) – Disposition (Treatment and Status) of Patients in Each Treatment Group on Day 84 – Intention to Treat Population

Treatment/ Status	Voriconazole (N=194)			Amphotericin B (N=185)		
	Study 602 (N=68) n (%)	Study 307 (N=126) n (%)	Total (N=194) n (%)	Study 602 (N=64) n (%)	Study 307 (N=121) n (%)	Total (N=185) n (%)
Randomized Treatment	28 (41.2)	57 (45.2)	85 (43.8)	0	2 (1.7)	2 (1.1)
OLAT	7 (10.3)	19 (15.1)	26 (13.4)	17 (26.6)	55 (45.5)	72 (38.9)
Lipid Amphotericin B preparations	3 (4.4)	4 (3.2)	7 (3.6)	3 (4.7)	9 (7.4)	12 (6.5)
Amphotericin B	2 (2.9)	1 (0.8)	3 (1.5)	2 (3.1)	6 (5.0)	8 (4.3)
Itraconazole	2 (2.9)	14 (11.1)	16 (8.2)	11 (17.2)	39 (32.2)	50 (27.0)
Combination OLAT	0	0	0	1 (1.6)	1 (0.8)	2 (1.1)
Post Treatment Follow-up	4 (5.9)	14 (11.1)	18 (9.3)	7 (10.9)	14 (11.6)	21 (11.4)
Died	24 (35.3)	31 (24.6)	55 (28.4)	35 (54.7)	43 (35.5)	78 (42.2)
Discontinued	5 (7.4)	5 (4.0)	10 (5.2)	5 (7.8)	7 (5.8)	12 (6.5)
Total	68 (100.0)	126 (100.0)	194 (100.0)	64 (100.0)	121 (100.0)	185 (100.0)

OLAT=Other Licensed Antifungal Therapy

Table 7-12 Global Comparative Aspergillosis Study (307/602) – Disposition (Treatment and Status) of Patients in Each Treatment Group on Day 84 – Modified Intention to Treat Population

Treatment/ Status	Voriconazole (N=144)			Amphotericin B (N=133)		
	Study 602 (N=58) n (%)	Study 307 (N=86) n (%)	Total (N=144) n (%)	Study 602 (N=49) n (%)	Study 307 (N=84) n (%)	Total (N=133) n (%)
Randomized Treatment	25 (43.1)	37 (43.0)	62 (43.1)	0	2 (2.4)	2 (1.5)
OLAT	5 (8.6)	17 (19.8)	22 (15.3)	15 (30.6)	42 (50.0)	57 (42.9)
Lipid amphotericin B preparations	3 (5.2)	3 (3.5)	6 (4.2)	3 (6.1)	8 (9.5)	11 (8.3)
Amphotericin B	1 (1.7)	1 (1.2)	2 (1.4)	2 (4.1)	5 (6.0)	7 (5.3)
Itraconazole	1 (1.7)	13 (15.1)	14 (9.7)	9 (18.4)	28 (33.3)	37 (27.8)
Combination OLAT	0	0	0	1 (2.0)	1 (1.2)	2 (1.5)
Post Treatment Follow-up	4 (6.9)	9 (10.5)	13 (9.0)	4 (8.2)	7 (8.3)	11 (8.3)
Died	20 (34.5)	22 (25.6)	42 (29.2)	26 (53.1)	30 (35.7)	56 (42.1)
Discontinued	4 (6.9)	1 (1.2)	5 (3.5)	4 (8.2)	3 (3.6)	7 (5.3)
Total	58 (100.0)	86 (100.0)	144 (100.0)	49 (100.0)	84 (100.0)	133 (100.0)

OLAT=Other Licensed Antifungal Therapy

On Day 84, a greater percentage of patients in the voriconazole treatment group were still receiving randomized therapy than in the amphotericin B group (43.8% *vs.* 1.1% in the

Intention to Treat population). Most patients in both treatment groups who were switched to OLAT received itraconazole.

The following two figures display the disposition of patients in the voriconazole and amphotericin B groups over time.

Figure 7-3 Global Comparative Aspergillosis Study (307/602) – Disposition over Time in Voriconazole-Treated Patients – Modified Intention to Treat Population

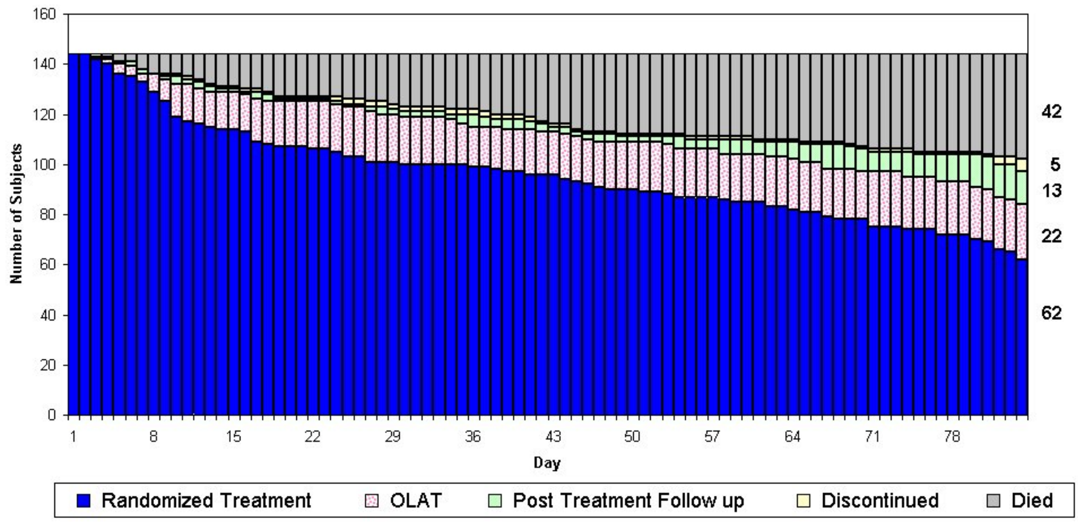
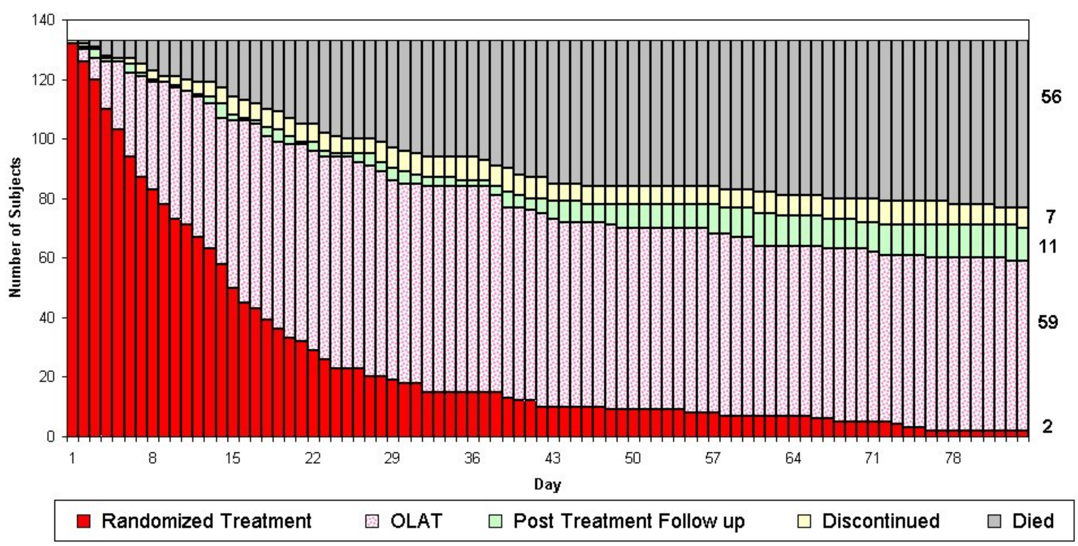


Figure 7-4 Global Comparative Aspergillosis Study (307/602) – Disposition over Time in Amphotericin B-Treated Patients – Modified Intention to Treat Population



Duration of Therapy

Table 7-13 and Table 7-14 show the duration of therapy in each treatment arm for the Intention to Treat and Modified Intention to Treat populations, respectively.

Table 7-13 Global Comparative Aspergillosis Study (307/602) – Duration of Therapy (Elapsed Time) of Initial Randomized Therapy and Treatment Regimen – Intention to Treat Population

Route of administration	Duration of Therapy (days)* Median (range)			
	Initial Randomized Treatment		Treatment Regimen	
	Voriconazole (N=194)	Amphotericin B (N=185)	Voriconazole/OLAT (N=194)	Amphotericin B/OLAT (N=185)
Intravenous	10 (2-90)	12 (1-85)	16 (2-130)	25 (1-26)
Oral	76 (2-232)	N/A	78 (2-232)	49 (1-128)
Total	74 (2-288)	12 (1-85)	87 (3-288)	57 (1-135)

OLAT = Other Licensed Antifungal Therapy; N/A = not applicable
*Elapsed time

Table 7-14 Global Comparative Aspergillosis Study (307/602) – Duration of Therapy (Elapsed Time) of Initial Randomized Treatment and Treatment Regimen – Modified Intention to Treat Population

Route of administration	Duration of Therapy (Days)* Median (range)			
	Initial Randomized Treatment		Treatment Regimen	
	Voriconazole (N=144)	Amphotericin B (N=133)	Voriconazole/OLAT (N=144)	Amphotericin B/OLAT (N=133)
Intravenous	11 (2-90)	11 (1-85)	16 (2-130)	27 (1-26)
Oral	75 (2-232)	N/A	79 (2-232)	49 (3-128)
Total	77 (2-288)	11 (1-85)	96 (3-288)	61 (1-135)

OLAT = Other Licensed Antifungal Therapy; N/A = not applicable
*Elapsed time

Voriconazole-treated patients in both the Intention to Treat and the Modified Intention to Treat populations received therapy longer than patients who received initial treatment with amphotericin B or patients who received the amphotericin B/OLAT treatment regimen. Patients randomized to amphotericin B received a mean daily dose of 1.0 mg/kg/day over the first 14 days of treatment.

Efficacy Evaluation

Primary Efficacy Analysis

The primary efficacy analysis was based on the Data Review Committee assessed global response at 12 weeks in the Modified Intention to Treat population (Table 7-15).

Table 7-15 Global Comparative Aspergillosis Study (307/602) – Data Review Committee-Assessed Outcome at Week 12 - Modified Intention to Treat Population

Outcome		Voriconazole (N=144)	Amphotericin B (N=133)
Success	Cure	30 (20.8)	22 (16.5)
	Improvement	46 (31.9)	20 (15.0)
	Total	76 (52.8)	42 (31.6)
Failure	Stable	8 (5.6)	8 (6.0)
	Failure	55 (38.2)	78 (58.6)
	Indeterminate	5 (3.5)	5 (3.8)
	Total	68 (47.2)	91 (68.4)

The results for outcome in the combined study populations are similar to the results in the individual studies, as shown in Table 7-16.

Table 7-16 Global Comparative Aspergillosis Study (307/602) - Data Review Committee-Assessed Outcome at Week 12 by Study - Modified Intention to Treat Population

Outcome*	Voriconazole			Amphotericin B		
	Study 602 (N=58) n (%)	Study 307 (N=86) n (%)	Total (N=144) n (%)	Study 602 (N=49) n (%)	Study 307 (N=84) n (%)	Total (N=133) n (%)
Success	27 (46.6)	49 (57.0)	76 (52.8)	11 (22.5)	31 (36.9)	42 (31.6)
Failure	31 (53.5)	37 (43.0)	68 (47.2)	38 (77.6)	53 (63.1)	91 (68.4)

*Success = cure or improvement; failure = stable, failure, indeterminate, or missing response

Death accounted for the major difference in failures between treatment arms. By Day 84, 42 voriconazole and 56 amphotericin B patients died (see Table 7-22 and Table 7-23).

The statistical analysis (adjusted by protocol) of the global response is shown in Table 7-17.

Table 7-17 Global Comparative Aspergillosis Study (307/602) – Data Review Committee-Assessed Outcome at Week 12 –Adjusted Analysis - Modified Intention to Treat Population

Outcome	Voriconazole (N=144)	Amphotericin B (N=133)	Difference Between Regimens	p value
Proportion of patients with success (adjusted*)	52.8%	30.6%	21.8%	<0.0001
95% CIs	44.70, 60.93	22.84, 38.30	10.54, 32.97	-

CI = confidence interval
Success = cure or improvement
*Adjusted by protocol

Because the lower limit of the approximate two-sided 95% confidence interval for the difference in success rates (voriconazole arm – amphotericin B arm) did not fall below –20%, the response to treatment in the voriconazole arm was considered to be non-inferior to the response in the amphotericin B arm. Moreover, since the confidence interval excludes 0, the voriconazole regimen is considered statistically superior to the amphotericin B regimen.

Randomization was stratified according to site of infection, underlying disease and neutrophil count. Table 7-18 depicts success according to the stratification factors and certainty of infection.

Table 7-18 Global Comparative Aspergillosis Study (307/602) – Data Review Committee-Assessed Week 12 Success by Stratification Factors and Certainty of Infection - Modified Intention to Treat Population

	Voriconazole (N=144)	Amphotericin B (N=133)	Difference Between Regimens (%)*	95% CI of Difference*
	Success n/N (%)			
Site of Infection				
Pulmonary	66/119 (55.5)	39/112 (34.8)	20.6	8.09, 33.19
Extra-pulmonary	10/25 (40.0)	3/21 (14.3)	25.7	1.37, 50.06
Underlying Disease				
Allogeneic BMT/PSCT	12/37 (32.4)	4/30 (13.3)	19.1	-0.28, 38.48
Autologous BMT/PSCT or hematological condition (e.g., leukemia)	51/81 (63.0)	32/84 (38.1)	24.9	10.09, 39.65
Other immunocompromised state (e.g., solid organ transplant, HIV/AIDS)	13/26 (50.0)	6/19 (31.6)	18.4	-9.97, 46.82
Neutrophil Count				
Neutropenic (ANC < 500 cells/mm^3)	32/63 (50.8)	19/60 (31.7)	19.1	2.07, 36.18
Non-neutropenic (ANC ≥ 500 cells/mm^3)	44/81 (54.3)	23/73 (31.5)	22.8	7.61, 38.02
Certainty of Infection				
Definite	30/67 (44.8)	8/41 (19.5)	25.3	8.27, 42.26
Probable	46/77 (59.7)	34/92 (37.0)	22.8	8.04, 37.52

ANC = absolute neutrophil count; CI = confidence interval; PSCT = peripheral stem cell transplant
*Difference between regimens and unadjusted confidence intervals

The above results were confirmed in the primary endpoint analysis applied to the Per Protocol population (not shown).

Secondary Efficacy Analyses

Success at End of Randomized Therapy

The rate of global success on voriconazole at the end of randomized therapy was greater than amphotericin B in the Modified Intention to Treat, Intention to Treat and Per Protocol populations. Table 7-19 summarizes the global responses at the end of randomized therapy.

Table 7-19 Global Comparative Aspergillosis Study (307/602) – Data Review Committee Assessed Outcome at End of Randomized Therapy - Modified Intention to Treat Population

Outcome		Voriconazole* (N=144) n (%)	Amphotericin B* (N=133) n (%)
Success	Cure	32 (22.2)	8 (6.0)
	Improvement	45 (31.3)	21 (15.8)
	Total	77 (53.5)	29 (21.8)
Failure	Stable	18 (12.5)	39 (29.3)
	Failure	41 (28.5)	53 (39.8)
	Indeterminate	8 (5.6)	12 (9.0)
	Total	67 (46.5)	104 (78.2)

*N.B. Median duration (elapsed time) of initial randomized therapy for voriconazole was 77 days, while that for amphotericin B patients was 11 days.

Data Review Committee-assessed success in the individual studies at End of Randomized Therapy is shown in Table 7-20.

Table 7-20 Global Comparative Aspergillosis Study (307/602) - Data Review Committee-Assessed Outcome at End of Randomized Therapy by Study - Modified Intention to Treat Population

Outcome*	Voriconazole			Amphotericin B		
	Study 602 (N=58) n (%)	Study 307 (N=86) n (%)	Total (N=144) n (%)	Study 602 (N=49) n (%)	Study 307 (N=84) n (%)	Total (N=133) n (%)
Success	27 (46.6)	50 (58.1)	77 (53.5)	11 (22.5)	18 (21.4)	29 (21.8)
Failure	31 (53.5)	36 (41.9)	67 (46.5)	38 (77.6)	66 (78.6)	104 (78.2)

*Success = cure or improvement; failure = stable, failure, indeterminate, or missing response
*N.B. Median duration of initial randomized therapy for voriconazole was 77 days, while that for amphotericin B patients was 10 days.

The adjusted statistical analysis for global response at End of Randomized Therapy is shown in Table 7-21.

Table 7-21 Global Comparative Aspergillosis Study (307/602) – Data Review Committee-Assessed Outcome at End of Randomized Therapy – Adjusted Analysis - Modified Intention to Treat Population

Outcome	Voriconazole (N = 144)	Amphotericin B (N = 133)	Difference between regimens	p value
Proportion of patients with success (adjusted)*	53.5%	21.8%	31.9%	<0.0001
95% CIs	45.4, 61.6	14.9, 28.8	21.2, 42.6	

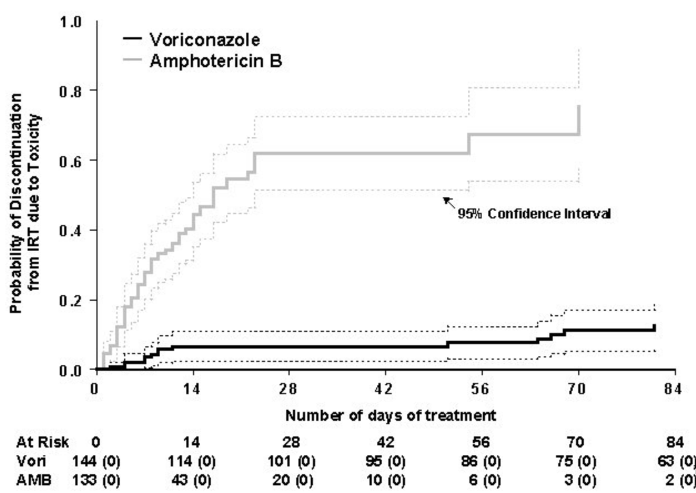
*Success = complete or partial response; failure = stable, failure, indeterminate, or missing response
*Adjusted by protocol

The better global response (as assessed by the Data Review Committee) in the voriconazole arm seen at Week 12 for the Modified Intention to Treat population was also observed at the end of randomized therapy. A higher proportion of patients in the voriconazole arm had a successful global response (complete or partial response as assessed by the Data Review Committee) at the end of randomized therapy compared with the patients in the amphotericin B arm. The difference in successful global response (adjusted by protocol) between the voriconazole and amphotericin B arms was 31.9% (95% confidence interval: 21.2, 42.6) in favor of voriconazole. It should be noted that there was a substantial difference in treatment duration at the end of randomized therapy, median duration for voriconazole-treatment patients was 77 days and median duration for amphotericin B-treated patients was 11 days.

Time to Discontinuation of Initial Randomized Therapy

Figure 7-5 displays a Kaplan-Meier plot of the time to discontinuation of Initial Randomized Therapy due to toxicity.

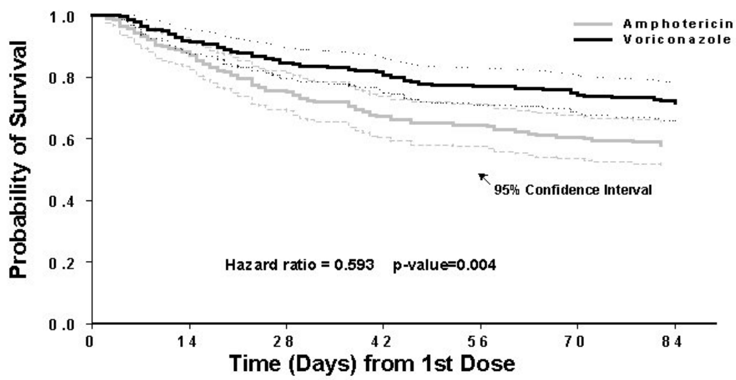
Figure 7-5 Global Comparative Aspergillus Study (307/602) – Kaplan – Meier Plot of Time to Discontinuation of Initial Randomized Therapy – Modified Intention to Treat Population



Survival

Voriconazole was associated with a survival advantage compared with amphotericin B as shown in Figure 7-6.

Figure 7-6 Global Comparative Aspergillosis Study (307/602) – Kaplan-Meier Plot of the Time to Death – Modified Intention to Treat Population



At Risk	0	14	28	42	56	70	84
Vori	194 (0)	177 (0)	164 (0)	156 (0)	149 (0)	139 (0)	144 (0)
AMB	185 (0)	161 (0)	139 (0)	124 (0)	119 (0)	112 (0)	107 (0)

By Day 84, 102 patients initially treated with voriconazole were still alive, compared with 77 amphotericin B patients. The difference in survival between the two treatment arms showed a hazard ratio (adjusted for protocol only) of 0.6 (95% confidence interval: 0.4, 0.9).

Data from the individual studies were consistent with the results of the combined analyses, as shown in Table 7-22.

Table 7-22 Global Comparative Aspergillosis Study (307/602) - Survival at Day 14 and Day 84 by Study - Modified Intention to Treat Population

Patient Status	Survival in Days From First Dose			
	Day 14		Day 84	
	Voriconazole/ OLAT n/N (%)	Amphotericin B/ OLAT n/N (%)	Voriconazole/ OLAT n/N (%)	Amphotericin B/ OLAT n/N (%)
Global Study				
Alive	131/144 (91.0)	117/133 (88.0)	102/144 (70.8)	77/133 (57.9)
Dead	13/144 (9.0)	16/133 (12.0)	42/144 (29.2)	56/133 (42.1)
Study 602				
Alive	54/58 (93.1)	41/49 (83.7)	38/58 (65.5)	23/49 (46.9)
Dead	4/58 (6.9)	8/49 (16.3)	20/58 (34.5)	26/49 (53.1)
Study 307				
Alive	77/86 (89.5)	76/84 (90.5)	64/86 (74.4)	54/84 (64.3)
Dead	9/86 (10.5)	8/84 (9.5)	22/86 (25.6)	30/84 (35.7)

The Data Review Committee assessed the causes of death for all patients who died. The causes of death for patients in the Modified Intention to Treat population are summarized in Table 7-23.

Table 7-23 Global Comparative Aspergillosis Study (307/602) – Data Review Committee-Assessed Cause of Death at Day 84 – Modified Intention to Treat Population

Cause of Death	Voriconazole/OLAT (N=144)	Amphotericin B/OLAT (N=133)
Alive at Day 84	102 (70.8)	77 (57.9)
Dead at Day 84	42 (29.2)	56 (42.1)
Death caused by aspergillosis	18 (12.5)	38 (28.6)
Death unrelated to aspergillosis but evidence of residual aspergillosis present	10 (6.9)	8 (6.0)
Death unrelated to aspergillosis and no evidence of residual aspergillosis	7 (4.9)	3 (2.3)
Indeterminate	7 (4.9)	4 (3.0)
Not assessed by Data Review Committee*	0	3 (2.3)

OLAT = Other Licensed Antifungal Therapy
*These 3 patients were not assessed because they died after withdrawal from the study.

Deaths due to or associated with aspergillosis accounted for most of the additional deaths seen on the amphotericin B arm.

Other Analyses

Outcome, using the global response assessed by the investigator at Week 12 and End of Randomized Therapy is shown in Table 7-24.

Table 7-24 Global Comparative Aspergillosis Study (307/602) – Outcome Using Investigator-Assessed Global Response at Week 12 and End of Randomized Therapy – Intention to Treat Population

Investigator-Assessed Global Response*	Voriconazole (N = 194) n (%)	Amphotericin B (N = 185) n (%)
Week 12		
Success	113 (58.2)	74 (40.0)
Failure	81 (41.8)	111 (60.0)
End of Randomized Therapy		
Success	112 (57.7)	58 (31.4)
Failure	82 (42.3)	127 (68.6)

*Success = cure or improvement; failure = stable, failure, indeterminate or missing

Mycology Assessment

Mycological assessment was performed on samples from patients in the Global Aspergillosis Study (307/602). Table 7-25 shows MIC_{50} and MIC_{90} values determined for the clinical isolates from this study.

Table 7-25 Global Comparative Aspergillosis Study (307/602) – *Aspergillus* MICs from Baseline Isolates

Organism	Number of Isolates	Antifungal Agent	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
A. fumigatus	160	Voriconazole	0.06 – 1.0	0.25	0.5
		Itraconazole	0.03 – 1.0	0.25	0.5
		Amphotericin B	0.2 – 2.0	1.0	2.0
A. niger	16	Voriconazole	0.125 – 1.0	0.25	1.0
		Itraconazole	0.06 – 0.5	0.5	0.5
		Amphotericin B	0.25 – 1.0	0.25	1.0
A. flavus	14	Voriconazole	0.125 – 0.5	0.25	0.5
		Itraconazole	0.03 – 0.25	0.12	0.25
		Amphotericin B	0.5 – 4.0	1.0	2.0
A. terreus	15	Voriconazole	0.125 - 1.0	0.25	1.0
		Itraconazole	0.005 – 0.25	0.12	0.25
		Amphotericin B	0.5 – 4.0	1.0	4.0
A. nidulans	5	Voriconazole	0.06 – 0.125		
		Itraconazole	0.06 – 0.25		
		Amphotericin B	0.5 – 1.0		
A. glaucus	1	Voriconazole	0.5		
		Itraconazole	0.5		
		Amphotericin B	4.0		
A. sydowii	1	Voriconazole	0.12		
		Itraconazole	0.12		
		Amphotericin B	2.0		

NCCLS M38-P Method, no established breakpoints for *Aspergillus* or other filamentous fungi (NCCLS 1998)

Of note, the susceptibility of the isolates from patients treated with voriconazole and patients treated with amphotericin B were similar, and, therefore, did not account for any differences in treatment effects.

<u>Summary of Efficacy Results</u>

Table 7-26 summarizes the efficacy results.

Table 7-26 Global Comparative Aspergillosis Study (307/602) – Summary of Efficacy Results - Intention to Treat (Investigator Assessment) and Modified Intention to Treat (DRC Assessment) Populations

	Intention to Treat		Modified Intention to Treat	
	Voriconazole (N=194) % with response	Amphotericin B (N=185) % with response	Voriconazole (N=144) % with response	Amphotericin B (N=133) % with response
Success* – Week 12 (Raw)	58.3	40.0	52.8	31.6
Success* – EORT (Raw)	57.7	31.4	53.5	21.8
Survival				
Alive at Day 14	91.2	87.0	91.0	88.0
Alive at Day 42	80.4	67.0	81.3	65.4
Alive at Day 84	71.6	57.8	70.8	57.9

EORT = end of randomized therapy
*Success = cure or improvement

7.1.1.8 Conclusions

The Global Comparative Aspergillosis Study (307/602) was a large comparative study conducted to investigate the initial treatment of immunocompromised patients diagnosed with acute invasive aspergillosis. The study met the protocol-specified criteria for efficacy and a higher proportion of voriconazole-treated patients had a successful outcome at Week 12, compared to the current standard therapy for invasive aspergillosis (amphotericin B, which was followed in this study by Other Licensed Antifungal Therapy). The treatment effect was also seen at the end of randomized therapy.

Kaplan-Meier plots show an early and continued survival benefit in favor of voriconazole. This treatment effect was consistent across both studies, seen in all analysis populations (Modified Intention to Treat, Intention to Treat, and Per Protocol) and in patients with poor prognostic factors such as allogeneic bone marrow transplant.

The comparative efficacy and survival benefits, as well as the favorable safety data (see Section 8), support the use of voriconazole for primary treatment of acute invasive aspergillosis.

7.1.2 Comparison of Non-Comparative Aspergillosis Study (304) and Contemporaneous Historical Control Study (1003)

7.1.2.1 Summary of Non-Comparative Aspergillosis Study (304)

The Non-Comparative Aspergillosis Study (304) was an open-label, uncontrolled, multi-center study of voriconazole for the treatment of acute invasive aspergillosis. This study was conducted in Europe from January 1994 to July 1996. The objective of the study was to assess the efficacy, safety and toleration of voriconazole in the treatment of acute invasive aspergillosis in immunocompromised patients. Patients with a diagnosis of definite or probable acute invasive aspergillosis (primary therapy) or with a diagnosis of definite acute invasive aspergillosis who had not responded to an adequate course of other antifungal therapy or were unable to tolerate previous antifungal therapy (salvage therapy) were eligible for the study. Eligible patients were to receive initial treatment with intravenous voriconazole at a dose of 6 mg/kg q 12 h for two doses, followed by 3 mg/kg q 12 h. Between Day 7 and Day 28 of intravenous therapy patients were to switch to oral voriconazole 200 mg bid. The total duration of treatment was to be a minimum of four weeks and a maximum of 24 weeks. In addition to the investigator evaluation of efficacy, a global response was assessed at End of Therapy by an external expert (Dr. David Denning, Manchester, United Kingdom) based on the Mycoses Study Group Criteria.

The primary efficacy endpoint was the clinical response as assessed by the investigator at the End of Therapy. Secondary efficacy endpoints included: clinical response at follow-up, clinical response by primary/salvage therapy (as defined by the investigator, Sponsor, and the external expert), clinical response at End of Therapy by prognostic factors such as: by whether the patients received five days or less of prior antifungal therapy or more than five days of prior antifungal therapy, baseline neutropenia, and by site of infection at baseline, mycological response, and time to death. Additional secondary endpoints included the external expert's assessment of global response, the external expert's assessment of global response by underlying disease, certainty of diagnosis, site of infection and baseline neutropenia. Patient survival was assessed at 30, 60 and 90 days from the start of voriconazole therapy. The analysis populations included Intention to Treat and Safety populations (including patients who received at least one dose of study treatment), Per Protocol population (including patients who fulfilled major inclusion criteria and had adequate assessments), and Expert Evaluable (as assessed by the external expert). Primary therapy patients were defined by the Sponsor, investigator and the external expert as those who had received less than 10 days of previous systemic antifungal drugs at therapeutic doses. While the same broad definition was used, assessments were not identical due to differing interpretation of what constituted therapeutic doses.

One hundred thirty seven patients received voriconazole and are included in the Intention to Treat and Safety populations. Thirty six patients were excluded from the Per Protocol population, primarily for lack of satisfactory diagnosis of aspergillosis at baseline (n = 31). Of these 31 patients, 11 had a probable diagnosis but received salvage voriconazole therapy (patients receiving salvage therapy were required to have a definite diagnosis). Twenty-five patients were excluded from the Expert Evaluable population, also primarily for lack of satisfactory diagnosis of aspergillosis at baseline (n = 20). Of the 137 patients who received treatment, 33 (24.1%) completed the study, 17 (12.4%) discontinued prematurely because of adverse events, 18 (13.1%) discontinued because of laboratory abnormalities, 40 (29.2%) patients died, and 7 (5.1%) patients discontinued due to lack of efficacy. There were 77 males and 60 females, with a mean age of approximately 45 years; 97.8% of patients were white. Most patients had underlying hematologic malignancy (65 patients, 47.4%), and approximately one third were neutropenic at baseline. The most frequent site of infection was pulmonary (101 patients, 73.7%).

As assessed by the investigator, 93 patients (67.9%) received voriconazole as primary therapy and 39 (28.5%) received voriconazole as salvage therapy, with 5 patients not classified. The median duration of IV therapy in all voriconazole-treated patients was eight days (range one to 39 days), the median duration of oral therapy was 53 days (range 2 to 219 days) and the median total duration of therapy was 44 days (range one to 246 days).

The primary efficacy analysis was the investigator assessment of clinical response at End of Therapy in the Intention to Treat population. These results, as well as the secondary efficacy analyses of End of Therapy clinical response in the Per Protocol and Expert Evaluable populations, are displayed in Table 7-27.

Table 7-27 Non-Comparative Aspergillosis Study (304) - Clinical Response At End of Therapy – Intention to Treat, Per Protocol, and Expert Evaluable Populations

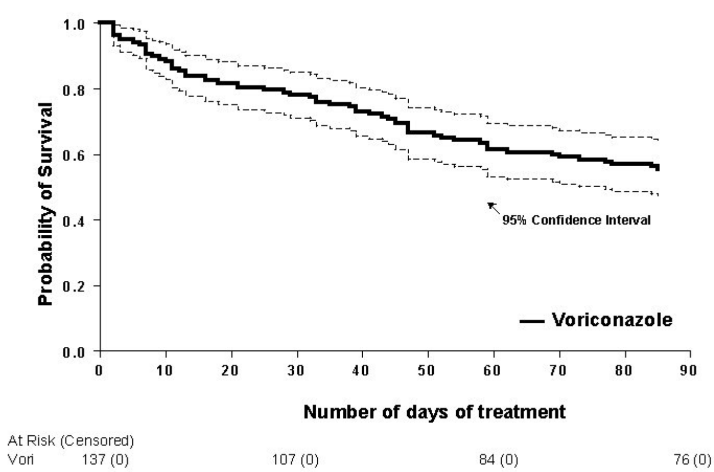
Response		Intention to Treat Population* (N=137) n (%)	Per Protocol Population* (N=101) n (%)	Expert Assessment (N=112)** n (%)
Success	Total	74 (54.0)	54 (53.5)	55 (49.1)
	Complete	49 (35.8)	37 (36.6)	16 (14.3)
	Partial	25 (18.2)	17 (16.8)	39 (34.8)
Failure	Total	63 (46.0)	47 (46.5)	57 (50.9)
	Stable	28 (20.4)	22 (21.8)	22 (19.6)
	Failure	33 (24.1)	24 (23.8)	34 (30.4)
	No evaluable data	2 (1.5)	1 (1.0)	1 (0.9)

*Investigator clinical response
**Expert global response

The overall success rates were similar regardless of the population studied, although the external expert categorized more responses as partial success and fewer as complete success.

This study also examined survival following initiation of study therapy for invasive aspergillosis. In the Intention to Treat analysis, 76/137 patients (55%) were alive at 90 days (after initiation of therapy). Figure 7-7 presents a Kaplan-Meier plot of survival.

Figure 7-7 Non-Comparative Aspergillosis Study (304) – Kaplan-Meier Plot of Time to Death – Intention to Treat Population



In the Non-Comparative Aspergillosis Study (304), 74 patients (54.0%) in the Intention to Treat population had a successful (complete and partial) response at the End of Therapy according to the investigator. The investigator and the external expert had broad agreement on the results of the study. The results for the Intention to Treat and Per Protocol populations were similar. Seventy-six patients (55%) survived to 90 days.

7.1.2.2 Summary of Historical Control Study (1003)

This study was an historical control survey designed to retrospectively collect global response and 90 day survival data for immunocompromised patients who received standard therapy for definite or probable acute invasive aspergillosis between January 1993 and December 1995, contemporaneous with the conduct of the Non-Comparative Aspergillosis Study (304). Data were obtained from a search of hospital records (Europe and the United States) and from an EORTC database. Relevant clinical data were collected for patients who had received antifungal agents including amphotericin B, lipid-associated formulations of amphotericin B, 5-flucytosine or oral itraconazole. The investigator retrospectively assessed the global response of each patient at End of Therapy according to one of four possible outcomes, complete response (cure), partial response (improvement), stable, and failure. Data on patient survival up to 90 days from study baseline and attribution of death (death caused by aspergillosis, death unrelated to aspergillosis, death with aspergillosis or indeterminate) were collected. Three hundred ninety six patients were screened and 257 (64.9%) patients were assessed as evaluable, that is patients without significant protocol violations.

7.1.2.3 Objectives of the Comparison between Study 304 and Study 1003

The objective of this comparison was to evaluate the response to therapy and 90 day survival in the Non-Comparative Aspergillosis Study (304) by comparing these endpoints in a matched set of patients from both datasets.

7.1.2.4 Study Design/Inclusion Criteria

The study design and inclusion criteria for Studies 304 and 1003 are outlined in the previous sections.

7.1.2.5 Statistical Methods

Efficacy Endpoints and Analyses

Primary Endpoint

The primary endpoints were survival (through 90 days after start of therapy) and successful global response at end of treatment. Success global response was defined as a complete response [cure] or partial response as assessed by the investigator.

It was prospectively defined that the primary analysis would not involve formal statistical methods or hypothesis testing. Therefore the primary analysis was a descriptive presentation of global response and survival in the case-matched population who had received five days or less of therapy. The percentage of satisfactory Global Responses in each treatment group was presented according to the various pre-defined matching and stratification criteria. In addition, 90-day survival was calculated using the product limit estimator obtained from the Kaplan-Meier plot. For both global response and 90 day survival, conclusions concerning the comparative efficacy of voriconazole *vs.* standard treatment were based upon clinical interpretation, since no statistical hypothesis testing was done.

Further analyses of the primary endpoints were prospectively defined: In order to explore robustness, the analyses were repeated for a different analysis population (< 10 days of prior therapy). In addition, a formal stratified statistical analysis of both global response (by logistic regression) and survival (by Cox proportional hazards modeling) was performed in all evaluable patients. This analysis was presented as an alternative method to case-matching, of adjusting the observed response rates for important prognostic factors. These analyses presented 95% confidence intervals for the ratio (voriconazole/historical control) of the odds of a satisfactory global response and the ratio of the hazard of death on each treatment. The analyses were stratified for sex, age category, underlying disease, site of infection, and certainty of disease.

Secondary Endpoints

Secondary endpoints defined in the statistical analysis plan were resolution of baseline neutropenia and emergence of graft *vs.* host disease. These endpoints were summarized by simple descriptive methods.

Analysis Populations

The primary analysis population was the 'Best Matched ≤ 5 Day Patients' population. The secondary analysis population was the 'Best Matched <10 Day Patients' population. These are defined in Table 7-28.

Table 7-28 Non-Comparative Aspergillosis Study (304) *vs.* Historical Control Study (1003) - Definitions of Analysis Populations

Population	Criteria
Best Matched ≤5 Day Patients	• Evaluable Study 1003 historical control patients who were matched with Per Protocol primary Study 304 patients who had received five days or less of prior antifungal therapy, with duration assessed by the Sponsor
Best Matched <10 Day Patients	• Evaluable Study 1003 historical control patients who were matched with Per Protocol primary Study 304 patients who received less than 10 days of prior antifungal therapy, with duration assessed by the Sponsor

Sample Size Determination and the Case-Matching Process

There was no formal sample size calculation performed for Study 1003. The aim was to case-match, on a 2:1 basis, using important prognostic criteria, 154 historical control patients to 72 patients from the Per Protocol population of Study 304. The Study 304 patients all received less than 10 days of prior antifungal treatment. In order to achieve the 2:1 match it was estimated that approximately 300 patients would be required.

Patients were case-matched on the prognostic factors of certainty of diagnosis, underlying disease and site of infection. The case-matching process was performed twice because two analysis populations were defined.

The matching process was performed using a computer program, which employed the algorithm exactly as defined in the statistical analysis plan. No manual intervention in the matching process was possible. Where there was an excess of 2:1 historical control to voriconazole patients within a risk factor combination, ties were broken by matching on age category, sex, presence of neutropenia and presence of graft *vs.* host disease at baseline.

Randomization and Stratification

There was no treatment randomization because the two groups represent separate historical cohorts. Patients were stratified for the analyses and case-matching as follows (Table 7-29).

Table 7-29 Historical Control Study 1003 - Stratification Factors Used in Case-Matching and Statistical Analyses

Stratification Variables	Details
Certainty of diagnosis	• Definite fungal infection • Probable fungal infection
Underlying disease	• Hematological malignancy • Bone marrow transplant • Other disease
Site of infection	• Systemic (non-brain) • Brain • Pulmonary • Other site

Statistical Analysis Plan

The statistical analysis plan was finalized on 4 January 2000, with a minor amendment on 17 January 2000 to update table shells. The analysis plan was finalized prior to the case-matching process.

Interim Analyses

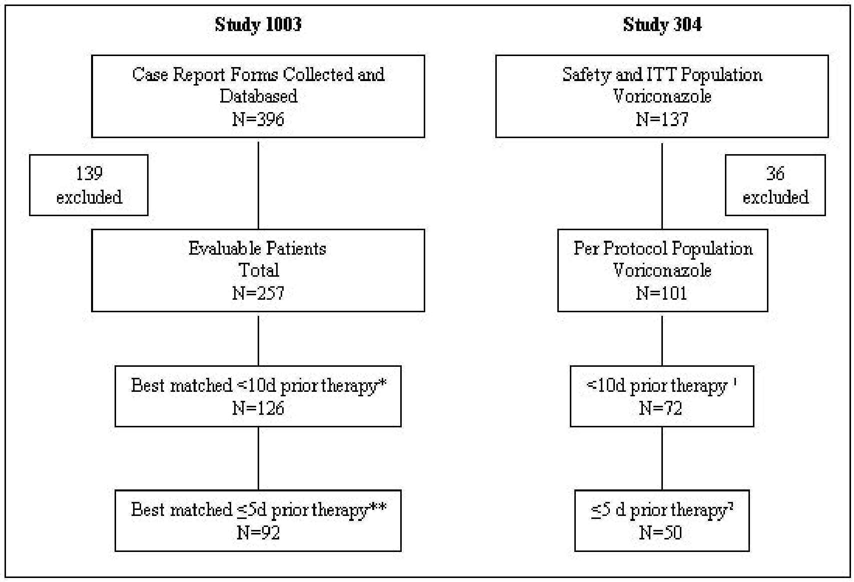
No interim analyses were performed. The case-matching and statistical analyses were performed only after the final database was released.

7.1.2.6 Results

Patient Disposition

Figure 7-8 displays the number of patients screened and assessed as evaluable in Study 1003, the derivation of matched patients and the derivation of patients from Study 304 used in the primary efficacy analysis.

Figure 7-8 Non-Comparative Aspergillosis Study (304) *vs.* Historical Control Study (1003) – Evaluation Groups



*Evaluable patients from historical and control study 1003 who were matched with all Study 304 Per Protocol primary therapy patients who received <10 days of prior anti-fungal treatment.

**Evaluable patients from historical control study 1003 who were matched with all Study 304 Per Protocol primary therapy patients who received ≤ 5 days of prior anti-fungal treatment.

[1]Per protocol patients from the 304 study who received <10days of prior anti-fungal treatment, with duration assessed by the sponsor.

[2]Per protocol patients from the 304 study who received ≤ 5days of prior anti-fungal treatment, with duration as assessed by the sponsor.

Baseline Characteristics/Demographics

The demographic characteristics of patients included in the comparison of Studies 304 and 1003 are presented in Table 7-30.

Table 7-30 Non-Comparative Aspergillosis Study (304) *vs.* Historical Control Study (1003) – Demographic Characteristics – Best Matched ≤5 Day Patients

Demographic Characteristic	Voriconazole Study 304			Historical Control Study 1003		
	Males (N=32)	Females (N=18)	Total (N=50)	Males (N=58)	Females (N=34)	Total (N=92)
Age range (years)	18-72	24-72	18-72	22-78	19-83	19-83
Mean	50.0	51.6	50.6	51.3	52.3	51.7
Weight range (kg)	45.0-97.0	47.0-79.5	45.0-97.0	55.0-97.7	43.5-110.0	43.5-110.0
Mean	70.9	60.2	67.1	74.2	65.6	71.0
Race n (%)						
White	31 (96.9)	18 (100.0)	49 (98.0)	40 (69.0)	28 (82.4)	68 (73.9)
Black	0	0	0	3 (5.2)	1 (2.9)	4 (4.3)
Asian	0	0	0	1 (1.7)	0	1 (1.1)
Other	1 (3.1)	0	1 (2.0)	14 (24.1)	5 (14.7)	19 (20.7)

Table 7-31 provides a summary of underlying disease, neutrophil status, and site of infection for all patients at baseline.

Table 7-31 Non-Comparative Aspergillosis Study (304) *vs.* Historical Control Study (1003) – Underlying Disease, Neutrophil Status, and Site of Infection at Baseline – Best Matched ≤5 Day Patients

Baseline Characteristic	Voriconazole Study 304 (N=50) n (%)	Historical Control Study 1003 (N=92) n (%)
Underlying Disease		
Allogeneic BMT/PSCT	11 (22)	16 (17.4)
Autologous BMT/PSCT	1 (2.0)	0
Hematological malignancy	26 (52.0)	52 (56.5)
Other immunocompromised state		
Other hematological condition (non-malignant)	0	2 (2.2)
HIV/AIDS	1 (2.0)	3 (3.3)
Solid organ transplant	0	5 (5.4)
Other solid organ malignancy	3 (6.0)	3 (3.3)
High dose corticosteroid therapy/other immunosuppressive therapy	0	3 (3.3)
Other	8 (16.0)	8 (8.7)
GvHD	7 (14.0)	6 (6.5)
Neutrophil Status		
Neutropenic	16 (32.0)	39 (42.4)
Non-neutropenic	33 (66.0)	47 (51.1)
Unknown	1 (2.0)	6 (6.5)
Site of Infection		
Pulmonary	41 (82.0)	82 (89.1)
Systemic (non-brain)	1 (2.0)	0
Brain	6 (12.0)	6 (6.5)
Other	2 (4.0)	4 (4.3)

AIDS = acquired immunodeficiency disease; BMT = bone marrow transplant; GvHD = graft *vs.* host disease; HIV = human immunodeficiency virus; PSCT=peripheral stem cell transplant

For the ≤ five day primary population in Studies 304 and 1003, the demographic data and baseline characteristics were well matched with the following exceptions: there was an imbalance in baseline neutrophil status, with a smaller proportion of neutropenic patients in the voriconazole 304 population (16/50, 32%) compared to the historical control population (39/92, 42.4%). There was a higher rate of baseline graft *vs.* host disease in voriconazole patients compared to that in the historical control population (14% *vs.* 7%) but it should be noted that for 15% of historical control patients, the presence of graft vs. host disease was unknown.

Treatment/Duration of Treatment

The treatments that patients in the historical control group received are summarized in Table 7-32.

Table 7-32 Non-Comparative Aspergillosis Study (304) *vs.* Historical Control Study (1003) – Antifungal Therapy Received by Historical Control Patients

Anti-fungal Therapy	Historical Control Evaluable Patients (N = 92)* n (%)
Amphotericin B	77 (83.7)
Itraconazole	48 (52.2)
Lipid preparations of amphotericin B	18 (19.6)
Liposomal amphotericin B	13 (14.1)
Amphotericin B lipid complex	2 (2.2)
Amphotericin B colloidal dispersion	3 (3.3)
Ketoconazole	1 (1.1)
5 Flucytosine	18 (19.6)

*Patients may have received more than one antifungal agent and, therefore, total is greater than 92 patients.

The duration of treatment in the primary therapy voriconazole patients (median 49 days, range 1 to 219 days, actual time) was longer than that for the historical controls (median 19 days, range 2 to 175 days, elapsed time).

Efficacy Evaluation

Outcome of the Matching Process

The overall matching ratio of historical control to voriconazole patients was approximately 1.8:1. Therefore the case matching process produced two historical control populations that were relatively well balanced with their respective Non-Comparative Aspergillosis Study (304) populations (<10 day and $\leq$5 days of prior antifungal treatment) for the categories of underlying disease, certainty of fungal diagnosis and site of infection.

Primary Efficacy Analyses

The global responses as assessed by the investigator at the End of Therapy in evaluable patients in the matched populations from the Non-Comparative Aspergillosis Study (304) and the Historical Control Study (1003) are summarized in Table 7-33.

Table 7-33 Non-Comparative Aspergillosis Study (304) *vs.* Historical Control Study (1003) – Investigator-Assessed Global Response at End of Therapy – Five Days or Less and Less than 10 Day Primary Populations

Outcome		Voriconazole* Study 304		Historical Control Study 1003	
		≤5 days prior therapy* (N=50) n (%)	<10 days prior therapy* (N=72) n (%)	≤5 days prior therapy* (N=92) n (%)	<10 days prior therapy* (N=126) n (%)
Success	Complete	17 (34.0)	28 (38.9)	14 (15.2)	20 (15.9)
	Partial	9 (18.0)	12 (16.7)	9 (9.8)	16 (12.7)
	Total	26 (52.0)	40 (55.6)	23 (25.0)	36 (28.6)
Failure	Stable	11 (22.0)	15 (20.8)	19 (20.7)	21 (16.7)
	Failure	13 (26.0)	17 (23.6)	50 (54.3)	69 (54.8)
	Total	24 (48.0)	32 (44.4)	69 (75.0)	90 (71.4)

*Duration of prior therapy as assessed by Sponsor.

Table 7-34 summarizes the survival in the primary analysis populations.

Table 7-34 Non-Comparative Aspergillosis Study (304) *vs.* Historical Control Study (1003) - Survival

	Voriconazole Study 304 (N=50) n (%)	Historical Control Study 1003 (N=92) n (%)
Alive at 90 days, n (%)	26 (52.0)	32 (34.8)
Dead, n (%)	22 (44.0)	52 (56.5)
Censored, n (%)	2 (4.0)	8 (8.7)
Probability of survival at 90 days	0.55	0.42
Approximate 95% confidence interval for survival	(0.42, 0.69)	(0.31, 0.52)

7.1.2.7 Conclusions

In the comparison of the results from the Non-Comparative Aspergillosis Study (304) and the Historical Control Study (1003), the objective of matching retrospective control patients, treated for aspergillosis in the same time frame, with voriconazole patients was achieved for the majority of the primary risk factor combinations. The response at End of Therapy and survival rate at 90 days for patients in the Non-Comparative Aspergillosis Study (304) compared favorably to that observed in the Historical Control Study (1003) patients**.**

7.1.3 Summary of Voriconazole Treatment of Aspergillosis

The randomized open label Global Comparative Aspergillosis Study (307/602) is a large comparative study conducted to investigate the initial treatment of immunocompromised patients diagnosed with acute invasive aspergillosis. The study met the protocol-specified criteria for efficacy and a higher proportion of voriconazole-treated patients had a successful outcome at Week 12, compared to the current standard therapy for invasive aspergillosis (amphotericin B, which was followed in this study by Other Licensed Antifungal Therapy). The treatment effect was also seen at the end of randomized therapy. Kaplan-Meier plots show an early and continued survival benefit in favor of voriconazole. This treatment effect was consistent across both studies, seen in all analysis populations (Modified Intention to Treat, Intention to Treat, and Per Protocol) and in patients with poor prognostic factors such as allogeneic bone marrow transplant.

In the Non-Comparative Aspergillosis Study (304), 74 patients (54.0%) in the Intention to Treat population had a successful (complete or partial) response at the End of Therapy according to the investigator. In the comparison of the results from the Non-Comparative Aspergillosis Study (304) and the Historical Control Study (1003), the response at End of Therapy and survival rate at 90 days for patients in the Non-Comparative Aspergillosis Study (304) compared favorably to that observed in the Historical Control Study (1003) patients**.**

Appendix 4 presents information from a pooled analysis of aspergillosis efficacy across the voriconazole clinical program (except the Global Comparative Aspergillosis Study [307/602], which was not available at the time of the original NDA submission). Information is presented on a total of 332 patients with confirmed *Aspergillus* infections, including patients with poor prognostic risk factors, such as central nervous system infections and allogeneic bone marrow transplants. Among the 45 patients with central nervous system involvement, 11 (24.4%) had successful outcome following voriconazole therapy.

The comparative efficacy and survival benefits shown in the randomized open label Global Comparative Aspergillosis Study (307/602), as well as the other supportive efficacy data and the favorable safety profile, support the use of voriconazole for primary treatment of acute invasive aspergillosis.

7.2 Empirical Therapy

The efficacy of voriconazole as empirical therapy is based on data supporting voriconazole's efficacy in treating documented fungal infections, including aspergillosis and *Candida* infections as well as on data from the controlled Empirical Therapy Study (603/MSG42). This randomized open label study compared voriconazole to liposomal amphotericin B as empirical antifungal therapy in patients with persistent fever and neutropenia. This study was conducted in the U.S., Canada, Europe, and India from March 1998 to September 1999.

7.2.1 Empirical Therapy Study (603/MSG42)

7.2.1.1 Study Objectives

The objectives of the study were to evaluate efficacy (non-inferiority), safety, and tolerability of voriconazole compared to liposomal amphotericin B for the empirical treatment of fungal infections in immunocompromised patients with persistent fever and neutropenia and to compare survival, frequency of breakthrough (BT) deeply invasive fungal infections (DIFI), and time to defervescence in patients treated with voriconazole or liposomal amphotericin B. This study was based on the earlier MSG32 study, which compared conventional amphotericin B with liposomal amphotericin B (Walsh, *et. al.* 1999).

7.2.1.2 Study Design

This was an open label, multi-center, randomized, comparative study of voriconazole *vs.* liposomal amphotericin B. Randomization was stratified for: risk of developing invasive fungal infection and use of systemic antifungal prophylaxis. High risk patients included those with allogeneic bone marrow transplant or relapsed leukemia and moderate risk patients included those with autologous transplants, newly diagnosed leukemia or other neoplasms.

Patients randomized to voriconazole were administered an intravenous (IV) loading dose of 6 mg/kg q 12 h for two doses followed by 3 mg/kg q 12 h, to be administered for a minimum of three days. After three days, voriconazole treatment could be given orally at a dose of 200 mg bid (100 mg bid for patients weighing <40 kg). Patients randomized to liposomal amphotericin B were administered an IV dose of 3 mg/kg/day IV. Both voriconazole and liposomal amphotericin B-treated patients were treated until three days after recovery from neutropenia (>250 cells/mm^3) or for up to 12 weeks in the event of confirmed baseline or breakthrough fungal infection. Dosage of either treatment could be increased in presence of a baseline or breakthrough deeply invasive fungal infections, persistence of fever and no improvement in baseline pulmonary infiltrates at least 24 hours after initiation of treatment, or persistence of fever and new pulmonary infiltrates at least 24 hours after initiation of treatment. Dosage could be decreased if the patient did not tolerate the escalated dose, according to protocol-specified criteria.

Following randomization, during the period of neutropenia and the treatment period after recovery from neutropenia, the investigator evaluated the patient daily for the presence of bacterial or fungal infection, body temperature, and absolute neutrophil count, according to protocol specifications. For patients who were not diagnosed with a baseline or breakthrough infection, a clinical evaluation was performed seven days after the End of Therapy (last dose of antifungal drug). The patient was classified as a success if investigator classified the patient as a success or failure according to the five criteria for success.

Patients with documented baseline or breakthrough infections were eligible to receive up to 12 weeks of therapy and had clinical evaluations every 4 weeks until the End of Therapy, at End of Therapy and 4 weeks after End of Therapy. At End of Therapy and 4 weeks after End of Therapy, the overall response was assessed by the investigator.

Table 7-35 Empirical Therapy Study (603/MSG42) – Overall Response Definitions

Criterion **Definition**	**Time point or period when assessed**	**Success** All five individual criteria had to be fulfilled:	**Failure** Any of these criteria fulfilled:
Survival	Through seven days following End of Therapy	Survival	Death
Breakthrough fungal infections Any deeply invasive fungal infection that is diagnosed based on results of tests performed more than 24 hours after study entry.	During neutropenia or within seven days after discontinuation of study medication	None	Documented
Defervescence Oral temperature <38.0°C for a continuous period of at least 48 hours preceding recovery from neutropenia (absolute neutrophil count ≤250 cells/mm^3)	Prior to recovery from neutropenia	Defervescence	Persistent fever
Discontinuation of study medication due to toxicity or lack of efficacy	Prior to recovery from neutropenia	No discontinuation due to toxicity or lack of efficacy	Discontinuation due to toxicity or lack of efficacy
Global Response (for patients with Baseline Infections*)	At end of therapy	Complete or Partial	Stable or Failure

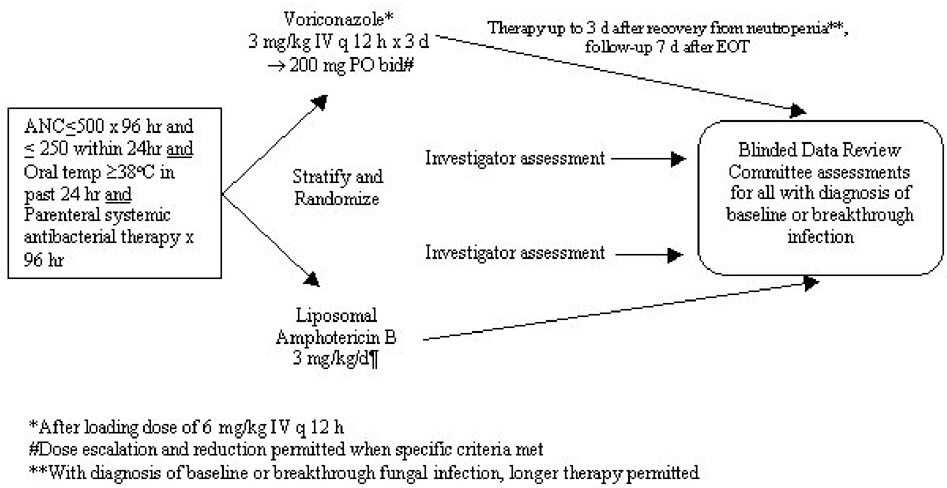
*Any deeply invasive fungal infection diagnosed based on results of tests performed at baseline or up to 24 hours after study entry.

For patients with documented baseline or breakthrough deeply invasive fungal infections, the investigator assessed the global response to treatment at End of Therapy and four weeks after End of Therapy as complete response, partial response, stable and failure. Infusions were prospectively monitored for signs of toxicity with bedside worksheets as specified in the protocol.

The National Institute of Allergy and Infectious Diseases Mycoses Study Group collaborated on this protocol. These collaborators used an independent Data and Safety Monitoring Board to perform regular safety analyses on the accumulating data and to perform an interim analysis of efficacy.

The study procedures are illustrated in Figure 7-9.

Figure 7-9 Empirical Therapy Study (603/MSG42) – Study Procedures



7.2.1.3 Key Entry Criteria

Eligible patients had neutropenia induced by cytotoxic chemotherapy or bone marrow/peripheral stem cell transplant; who had received >96 hours of parenteral systemic antibacterial therapy, while remaining persistently febrile (oral temperature ≥38°C within 24 hours of randomization) and neutropenic (absolute neutrophil count ≤500 cells/mm^3 for at least 96 hours and ≤250 cells/mm^{3}within 24 hours of randomization). Patients were not eligible for the study if they had documented deeply invasive fungal infection at the time of randomization. Important exclusion criteria included: alanine transaminase, aspartate transaminase, or alkaline phosphatase above five times the upper limit of normal, serum creatinine >2.5 mg/dL, life expectancy less than 72 hours, and administration of excluded concomitant medications.

7.2.1.4 Statistical Methods

Efficacy Endpoints and Analyses

Primary Endpoint

The primary endpoint was overall response assessed seven days after End of Therapy. Overall response was a composite of five prospectively-defined secondary endpoints: survival, absence of breakthrough fungal infection, no discontinuation due to toxicity or lack of efficacy, defervescence prior to recovery from neutropenia, and, for patients with baseline fungal infections only: successful global response at End of Therapy.

The prospectively defined analysis of the primary endpoint entailed the construction of a stratified 95% confidence interval for the difference in the overall response rate between treatments in the Modified Intention to Treat population. The confidence interval was derived from a method of linear stratification that was weighted according to the reciprocal of the variance. The analysis included terms for prior duration of neutropenia and the two randomization strata: risk of fungal infection and previous systemic antifungal prophylaxis. The confidence interval was compared with a non-inferiority margin of –10%.

Secondary Endpoints

Secondary endpoints were defined in the protocol as: fever response (defervescence) during neutropenia, frequency of breakthrough deeply invasive fungal infections, global response, time to death, time to discontinuation of study medication due to toxicity (subsequently amended in the statistical analysis plan to also include discontinuation due to lack of efficacy), and time to defervescence. Further endpoints were defined in the statistical analysis plan as: overall response rate by potential prognostic factors, time to recovery from neutropenia , time to discontinuation of study medication due to toxicity or lack of efficacy prior to recovery from neutropenia, and, finally, a comparison of outcome of each of the five components of the overall response.

Basic summary statistics were produced for all secondary endpoints. For the five survival-type secondary endpoints, cumulative survival Kaplan-Meier curves were constructed and the treatment effect (hazard ratio and 95% confidence interval) was estimated from a stratified Cox proportional-hazards model. For the binary-type secondary endpoint frequency of breakthrough deeply invasive fungal infections, response rates were compared by Fishers exact test and stratified logistic regression. In addition, each component of the overall response was summarized by an unstratified 95% confidence interval for the difference in rates between treatments. Further analyses of the efficacy endpoints on pre-planned subgroups of patients were carried out.

Analysis Populations

The primary analysis population was a Modified Intention to Treat population. In order to address the guidance given in International Conference on Harmonization E-9 concerning appropriate analysis populations for non-inferiority trials, the Per Protocol population was defined to explore the robustness of the results of the primary analysis. The definitions of the two populations are given in Table 7-36.

Table 7-36 Empirical Therapy Study (603/MSG42) – Analysis Populations

Population	Criteria
Safety	• All patients who received at least one dose of randomized study medication
Modified Intention to Treat	• All patients who received at least one dose of randomized study medication • Had sufficient clinical information to confirm the investigator's assessment of overall response (e.g. patient's survival status, information relevant to breakthrough infection from the case report form or source document, temperature log, absolute neutrophil count log, information sufficient to confirm the investigator's assessment of global response, for those patients who had baseline infections
Per Protocol	• All patients who received at least one dose of randomized study medication • Had sufficient clinical information to confirm the investigator's assessment of overall response (e.g. patient's survival status, information relevant to breakthrough infection from the case report form or source document, temperature log, absolute neutrophil count log, information sufficient to confirm the investigator's assessment of global response, for those patients who had baseline infections • Had fever and neutropenia at baseline according to strict application of protocol-specified quantitative entry criteria by Sponsor • Had prior systemic antibacterial therapy according to strict application of protocol-specified quantitative entry criteria by Sponsor

Sample Size Determination

The sample size was based upon the following: a non-inferiority criterion which required that the lower bound of the 95% confidence interval of the difference in success rates was greater than -10%; an expected overall success rate of 50% in both treatment groups (as seen in a previous study comparing liposomal amphotericin B to amphotericin B in empirical treatment [Walsh 1999]), an expected 10% of the patients enrolled would be excluded from the modified Intention to Treat population, and the study would have 80% power to show non-inferiority at the two-sided 5% level of significance. Therefore, the study was designed to enroll a total of 866 patients (433 per treatment group).

Randomization and Stratification

Patients were randomized to receive either voriconazole or liposomal amphotericin B (1:1 ratio) via a central tele-randomization system (operated by Quintiles, North Carolina). The randomization was stratified according to previous systemic antifungal prophylaxis and risk of developing fungal infection.

Table 7-37 Empirical Therapy Study (603/MSG42) – Stratification Factors Used In Randomization

Stratification Variables	Details
Previous systemic antifungal prophylaxis	Yes or No
Risk of fungal infection	High Risk - allogeneic bone marrow transplant - allogeneic peripheral stem cell transplant - relapsed leukemia *vs.* Moderate Risk - autologous bone marrow transplant - autologous peripheral stem cell transplant - newly diagnosed leukemia - other neoplasm

Statistical Analysis Plan

The statistical analysis plan was finalized on 30 September 1999, with an amendment on 22 February 2000, prior to database release. The amendment provided more detailed definitions of terms used in the analyses, added a new secondary endpoint (time to discontinuation of study medication due to toxicity or lack of efficacy prior to recovery from neutropenia) and clarified the algorithms used to derive certain secondary endpoints.

Interim Analyses

An external Data Safety Monitoring Board, convened by the National Institute of Allergy and Infectious Diseases Mycoses Study Group, monitored safety data throughout the study. The Data Safety Monitoring Board was also conducted a protocol-specified 50% interim efficacy analysis, testing for statistical superiority in the overall response to therapy endpoint. However, due to rapid recruitment, the MSG proposed an earlier interim analysis which was performed in April 1999 including 348 (40% of target) completed patients. The Data Safety Monitoring Board was empowered to recommend early termination of the study if it observed a treatment effect on overall response that exceeded the stopping boundary as defined by the Lan and De Mets alpha-spending function. The interim results were not presented to the sponsor and no changes to the study design or conduct were recommended by the DSMB as a result of the interim analysis. There was no effect of the interim test for superiority on the type I error in the final non-inferiority analysis, therefore no p-value adjustments were necessary.

7.2.1.5 Data Review Committee

All patients with potential diagnoses of deeply invasive fungal infections (both baseline and breakthrough) were evaluated by the blinded Data Review Committee. The Data Review Committee assessed each patient for the presence of infection, type of infection (baseline or breakthrough), certainty of infection (definite or probable), and made a blinded assessment of global response at the End of Therapy. These blinded outcome assessments were made without any information regarding the investigators' assessments or treatment assignment. The blinded Data Review Committee assessment was incorporated into the primary analysis of the overall response and overrode the investigators' assessments in the event of a difference of opinion.

7.2.1.6 Protocol Amendments

The first amendment (24 March 1998) occurred shortly after the study start (7 March 1998) and included the following protocol changes which affected entry criteria, efficacy or safety assessments:

- In the original protocol, criteria were given for proven, probable, and possible baseline and breakthrough infections. In the amendment the category "possible" was deleted, after discussion of the protocol with FDA.
- The infusion-related reactions bedside worksheet was modified (addition of check boxes for study treatment and for the reporting of no signs or symptoms, chills and rigors were combined into a single category and definitions were provided for mild, moderate, severe and life threatening).

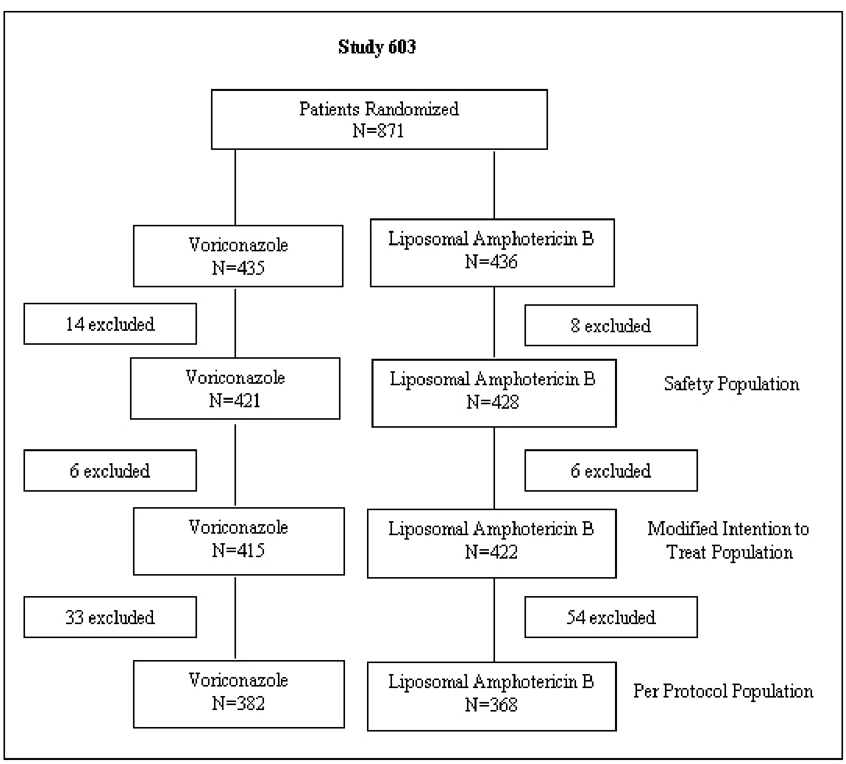
In April 1999 (approximately five months prior to the end of the study [September 1999]), a letter was distributed to investigators prohibiting the enrollment of patients at risk for cardiac arrhythmia.

7.2.1.7 Results

Patient Disposition

The disposition of enrolled patients is summarized in Figure 7-10.

Figure 7-10 Empirical Therapy Study (603/MSG 42) – Evaluation Groups



The reasons for exclusion from the Safety and Modified Intention to Treat populations are shown in Table 7-38. The Per Protocol population results are not presented in this Briefing Document and are not included in this table.

Table 7-38 Empirical Therapy Study (603/MSG42) - Reasons for Exclusion from the Modified Intention to Treat Population

Analysis Population Reason for Exclusion	Voriconazole Randomized (N = 435) Number excluded from population	Liposomal amphotericin B Randomized (N = 436) Number excluded from population
Safety		
Did not receive study drug	14	8
Modified Intention to Treat		
No confirmation of no breakthrough at least 7 days after End of Therapy	1	0
No on-treatment temperatures	2	2
Randomization issues (dosed before randomized, randomized twice and received different treatment on second dosing)	3	4
Total	6	6

Table 7-39 presents the disposition of patients.

Table 7-39 Empirical Therapy Study (603/MSG42) – Patient Disposition**

	Voriconazole N (%)	Liposomal amphotericin B N (%)
Received Treatment	421 (100.0)	428 (100.0)
Completed the study	310 (73.6)	335 (78.3)
Discontinued the study	111 (26.4)	93 (21.7)
Discontinued due to AE	33 (7.8)	30 (7.0)
Discontinued due to laboratory abnormality	10 (2.4)	8 (1.9)
Death	19 (4.5)	21 (4.9)
Lack of efficacy	27 (6.4)	6 (1.4)
Other*	22 (5.2)	28 (6.5)

AE = adverse event
*Other includes protocol violation (n=0 voriconazole, n=4 liposomal amphotericin B), lost to follow-up (n=2 voriconazole, n=1 liposomal amphotericin B), did not meet randomization criteria (n=2 voriconazole, n=1 liposomal amphotericin B), withdrawn consent (n=6 voriconazole, n=9 liposomal amphotericin B) and other miscellaneous reasons (n=12 voriconazole, n=13 liposomal amphotericin B).
**Per study summary page on case report form

Baseline Characteristics/Demographics

The demographic characteristics of voriconazole-treated patients are shown in Table 7-40.

Table 7-40 Empirical Therapy Study (603/MSG42) – Demographic Characteristics - Safety Population

	Voriconazole (N = 421)			Liposomal amphotericin B (N = 428)		
	Males (N=237)	**Females (N=184)**	**Total (N=421)**	**Males (N=219)**	**Females (N=209)**	**Total (N=428)**
Age range (years)	12 - 79	12 - 82	12 – 82	12 - 80	12 – 77	12 – 80
Mean	47.3	45.1	46.3	44.4	45.6	45.0
Weight range (kg)	29.6 – 150.0	40.0 - 199.6	29.6 –199.6	30.8 -155.0	32.0 -120.8	30.8 -155.0
Mean	79.7	71.0	75.9	78.7	68.6	73.7
Race n (%)						
White	178 (75.1)	150 (81.5)	328 (77.9)	171 (78.1)	165 (78.9)	336 (78.5)
Black	19 (8.0)	18 (9.8)	37 (8.8)	15 (6.8)	19 (9.1)	34 (7.9)
Asian	26 (11.0)	3 (1.6)	29 (6.9)	14 (6.4)	9 (4.3)	23 (5.4)
Hispanic	10 (4.2)	11 (6.0)	21 (5.0)	17 (7.8)	11 (5.3)	28 (6.5)
Other	4 (1.7)	2 (1.1)	6 (1.4)	2 (0.9)	5 (2.4)	7 (1.6)

All randomized patients had persistent fever and neutropenia. Table 7-41 provides a summary of baseline characteristics for all randomized patients at baseline.

Table 7-41 Empirical Therapy Study (603/MSG42) – Baseline Characteristics - Safety Population

Clinical Characteristics	**Voriconazole (N = 421) n (%)**	**Liposomal amphotericin B (N= 428) n (%)**
Underlying Disease		
Lymphoma	58 (13.8)	64 (15.0)
Multiple myeloma	22 (5.2)	25 (5.8)
Newly diagnosed leukemia	132 (31.4)	132 (30.8)
Other	62 (14.7)	63 (14.7)
Relapsed leukemia	94 (22.3)	86 (20.1)
Solid organ malignancy*	53 (12.6)	58 (13.6)
Bone Marrow Transplant		
Total	202 (48.0)	220 (51.4)
Allogeneic BMT	43 (10.2)	42 (9.8)
Allogeneic PSCT	36 (8.6)	37 (8.6)
Autologous BMT	11 (2.6)	17 (4.0)
Autologous PSCT	112 (26.6)	125 (29.2)
Risk Category		
High	146 (34.7)	143 (33.4)
Moderate	275 (65.3)	285 (66.6)
Duration of Neutropenia Prior to Randomization		
Median in days (range)	7.7 (2.4 – 71.5)	7.6 (2.4 – 59.7)

ANC = absolute neutrophil count; BMT = bone marrow transplant; PSCT = peripheral stem cell transplant
*Includes solid organ tumors

Four hundred and eighteen of 421 voriconazole patients (99.3%) and 422 of 427 liposomal amphotericin B patients (98.8%) had a documented absolute neutrophil count ≤ 250 cells/mm^3. Two hundred and twenty seven of 421 voriconazole patients (53.9%) and 255 of 428 liposomal amphotericin B patients (59.6%) received prior systemic antifungal prophylaxis. The antifungal agent was fluconazole in 184 of 227 voriconazole patients who received prophylaxis (81.1%) and 207 of 255 liposomal amphotericin B patients who received prophylaxis (81.2%).

Duration of Therapy

Table 7-42 shows the duration of therapy in each treatment arm.

Table 7-42 Empirical Therapy Study (603/MSG42) – Duration of Therapy – Safety Population

Route of Administration	Duration of Therapy (days)** Median (range)	
	Voriconazole (N=421)	Liposomal amphotericin B (N=428)
Intravenous	6 (1 - 46)	7 (1 - 84)
Oral*	6 (1 - 95)	N/A
Total duration of therapy	7 (1 -113)	7 (1 - 84)

N/A = not applicable
*92 voriconazole-treated patients received oral therapy.
**Elapsed time

Efficacy Evaluation

Primary Efficacy Analysis

Overall success rates (raw and stratified) based on the analysis of the composite of the five components of the primary efficacy endpoint are depicted in Table 7-43.

Table 7-43 Empirical Therapy Study (603/MSG42) - Overall Response to Empirical Therapy – Primary Analysis of Composite Outcome – Modified Intention to Treat Population

	Voriconazole (N=415)	Liposomal Amphotericin B (N=422)
Success (raw data) n (%)	108 (26.0)	129 (30.6)
Difference between voriconazole and liposomal amphotericin B (95% CI)	-4.5% (-10.6, 1.6)	
Success (stratified) (%)	23.7	30.1
Difference between voriconazole and liposomal amphotericin B (95% CI)	-6.1 (-12.0, -0.1)	

The raw and the stratified success rates (adjusted for risk of infection, previous systemic prophylaxis, and duration of baseline neutropenia) are presented together with the approximate two-sided 95% confidence intervals. The lower limit of the confidence interval was below –10% for both the raw and stratified analyses; therefore, voriconazole did not demonstrate non-inferiority.

The above results were confirmed in the primary endpoint analysis applied to the Per Protocol population (not shown).

Secondary Efficacy Analyses

Table 7-44 presents the results of the components of the composite endpoint for the Modified Intention to Treat population.

Table 7-44 Empirical Therapy Study (603/MSG42) – Overall Response and Response by Component – Modified Intention to Treat Population

Response Parameters	Voriconazole (N=415) n/N (%)	Liposomal amphotericin B (N=422) n/N (%)	Point estimate (Raw) 95% CI
Overall response to empirical therapy	108/415 (26.0)	129/422 (30.6)	-4.5 (-10.6, 1.6)
No breakthrough fungal infections within 7 days of End of Therapy	407/415 (98)	401/422 (95)	+3.1 (0.6, 5.5)
Survival through 7 days of End of Therapy	382/415 (92)	397/422 (94)	-2.0 (-5.5, 1.4)
No discontinuation due to toxicity or lack of efficacy before recovery from neutropenia	374/415 (90)	394/422 (93)	-3.2 (-7.0, 0.5)
Resolution of fever during neutropenia	135/415 (33)	154/422 (36)	-4.0 (-10.4, 2.5)
Global response of baseline fungal infections at End of Therapy (Complete or partial response)	6/13 (46)	4/6 (67)	-20.5 (-67.0, 25.9)

The lower than expected overall success in both treatment arms was due to the failure of many patients to defervesce before recovery from neutropenia. This is discussed in greater detail below (see Defervescence, below).

Each of the five components of the primary endpoint is discussed individually in this section.

Breakthrough Fungal Infections

There were eight of 415 voriconazole-treated patients (1.9%) and 21 of 422 liposomal amphotericin B-treated patients (5.1%) with documented breakthrough infections. Breakthrough fungal infections were prospectively defined in the protocol according to modified Mycoses Study Group criteria and each infection was reviewed by the blinded Data Review Committee. Only definite and probable infections were included in the analysis. Table 7-45 depicts each documented breakthrough invasive fungal infection.

Table 7-45 Empirical Therapy Study (603/MSG42) - Documented Breakthrough Fungal Infections – Modified Intention to Treat Population

Organism and Site	Voriconazole (n=415) n	Liposomal amphotericin B (N=422) n
Aspergillus	**4**	**13**
Lung	4	9
Sinuses	0	2
CNS/skin	0	1
Disseminated	0	1
Candida	**2**	**6**
Disseminated	1	0
Blood	1	6
Zygomycetes	**2**	**0**
Lung	1	0
Nasal	1	0
Dematiaceous moulds	**0**	**2**
Blood	0	1
Lung	0	1
Total	**8**	**21**

Four cases of aspergillosis occurred in voriconazole treated patients in comparison to 13 cases in liposomal amphotericin B treated patients. There were two cases of invasive candidiasis in the voriconazole arm in comparison to six in the liposomal amphotericin B arm.

Deaths

In the Modified Intention to Treat population, there were 58 patients who died within seven days of End of Therapy, 33 voriconazole-treated patients (8.0%) and 25 liposomal amphotericin B-treated patients (5.9%). There were no treatment differences in the Kaplan-Meier analysis.

Discontinuations due to Toxicity or Lack of Efficacy

As presented in Table 7-46, in the Modified Intention to Treat population, 41 voriconazole-treated patients (9.9%) and 28 liposomal amphotericin B-treated patients (6.6%) discontinued due to toxicity or lack of efficacy prior to recovery from neutropenia. Of note, this endpoint only addressed permanent discontinuations from study medication. The temporary discontinuations from liposomal amphotericin B were not included in this component of the endpoint. There were fewer temporary discontinuations on the voriconazole treatment arm (7) than in the liposomal amphotericin B treatment arm (38). An additional 14 liposomal amphotericin B patients underwent dose reductions prior to recovery from neutropenia.

Table 7-46 Empirical Therapy Study (603/MSG42) - Discontinuations due to Toxicity or Lack of Efficacy Prior to Recovery from Neutropenia – Modified Intention to Treat Population

	Voriconazole (N=415) n (%)	Liposomal amphotericin B (N=422) n (%)
Discontinuation due to toxicity or lack of efficacy prior to recovery from neutropenia	41 (9.9)	28 (6.6)
Discontinuation due to toxicity	19 (4.6)	23 (5.5)
Discontinuation due to lack of efficacy	22* (5.3)	5 (1.2)

*One patient discontinued due to both lack of efficacy and toxicity

Toxicity-related reasons for discontinuation included hepatic enzymes increased, liver function tests abnormal, liver damage, SGOT/SGPT increased (preferred terms) in three voriconazole patients and two liposomal amphotericin B patients.

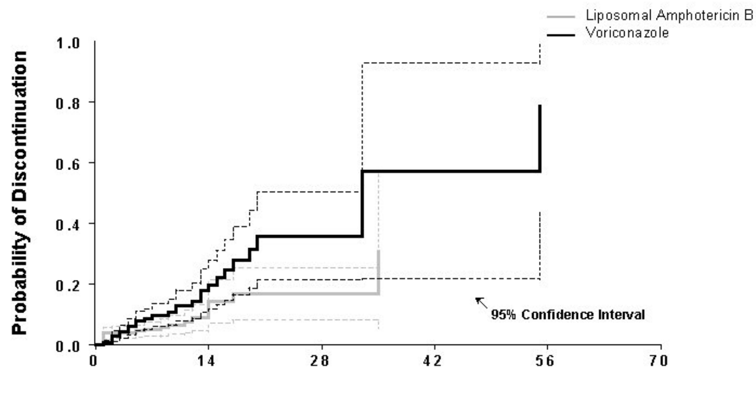
With respect to renal related reasons for discontinuation, acute kidney failure or kidney function abnormal (preferred terms) was reported as the reason for discontinuation in five voriconazole patients and no patients in liposomal amphotericin B patients.

In voriconazole-treated patients, the most frequent reasons for discontinuation due to toxicity, other than hepatic and renal related reasons, occurring in more than one patient, included: hallucinations (n = 3), dementia (n = 2), hypotension (n = 2), and rash (n = 3). In liposomal amphotericin B-treated patients, these reasons include: anaphylactoid reaction/shock (n = 6), vasodilatation (n = 5), dyspnea (n = 5), rash (n = 3), nausea/vomiting (n = 3), chest pain (n = 2), tachycardia (n = 2), asthma (n = 2), and cough increased (n = 2). More than one reason for discontinuation could be reported for each patient.

Twenty-two voriconazole patients (5.3%) compared to five liposomal amphotericin B patients (1.2%) discontinued prior to recovery from neutropenia due to lack of efficacy. Of note, six of 22 voriconazole-treated patients who discontinued due to lack of efficacy were from a single center.

Figure 7-11 displays time to discontinuation due to toxicity or lack of efficacy.

Figure 7-11 **Empirical Therapy Study (603/MSG42) - Kaplan-Meier Plot of Time to Discontinuation due to Toxicity or Lack of Efficacy Prior to Recovery from Neutropenia – Modified Intention to Treat Population**



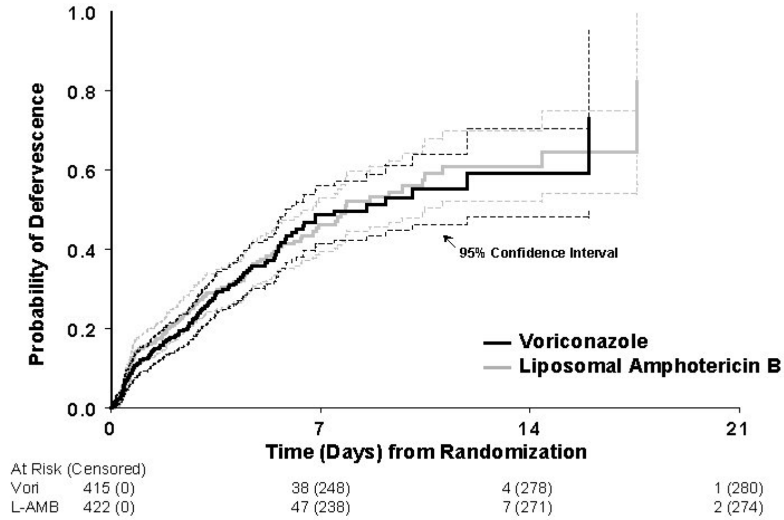
At Risk (Censored)						
Vori	415 (0)	34 (347)	6 (370)	2 (373)	1 (373)	0 (374)
L-AMB	422 (0)	43 (353)	12 (383)	1 (393)	1 (393)	0 (394)

Defervescence

Resolution of fever prior to recovery from neutropenia occurred in 135 of voriconazole-treated patients (33%) and 154 of liposomal amphotericin B-treated patients (36%) in the Modified Intention to Treat population.

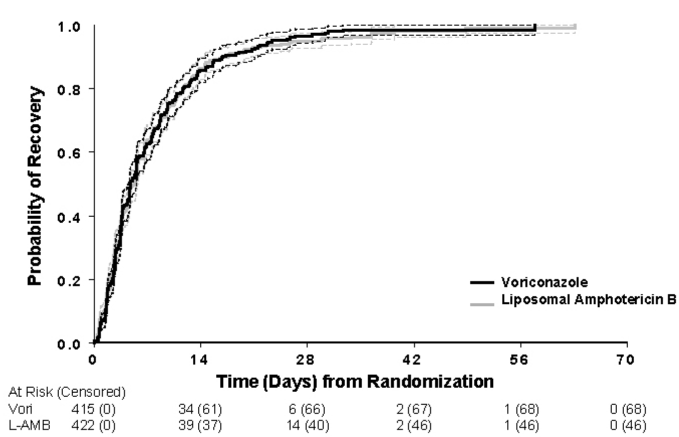
Failure to defervesce (to a temperature < 38.0°C or 100.4°F) for a continuous period of at least 48 hours preceding recovery from neutropenia was the most common reason for failure (overall response) in both treatment arms of the study. There was no significant difference in time to defervescence between treatment arms as depicted in the Kaplan-Meier analysis in Figure 7-12.

Figure 7-12 Empirical Therapy Study (603/MSG42) - Kaplan-Meier Plot of Time to Defervescence Prior to Recovery from Neutropenia – Modified Intention to Treat Population



This failure to defervesce was likely related to a shorter than expected duration of neutropenia seen in this study. A Kaplan-Meier plot of the time to recovery from neutropenia is provided in Figure 7-13.

Figure 7-13 Empirical Therapy Study (603/MSG42) - Kaplan-Meier Plot of Time to Recovery from Neutropenia – Modified Intention to Treat Population



The median time to recovery from neutropenia was 4.8 days in the voriconazole arm and 5.4 days in the liposomal amphotericin B arm, shorter than the 8 days seen in the liposomal amphotericin B patients treated in MSG32 (Mycoses Study Group communication). Patients thus had less time to defervesce prior to recovering from neutropenia in the current study. This may reflect changes in chemotherapeutic regimens and bone marrow transplantation since the earlier Mycoses Study Group trial (Walsh, *et. al.*, 1999). While cytotoxic chemotherapy has become more aggressive, the advent of peripheral stem cell infusions and equally aggressive use of growth factors have significantly reduced the period of neutropenia after chemotherapy.

The high failure rate in this aspect of the composite endpoint led to the higher than anticipated overall failure rate of 74.0% and 69.4% in the voriconazole and liposomal amphotericin B arms, respectively.

Baseline Fungal Infections

There was no significant difference in successful response to treatment of baseline fungal infections between voriconazole and liposomal amphotericin B therapy as shown in Table 7-47.

Table 7-47 Empirical Therapy Study (603/MSG42) - Response to Treatment by Baseline Infection – Modified Intention to Treat Population

	Success/Total n/N	
	Voriconazole (N=13)	**Liposomal amphotericin B (N=6)**
Baseline Infections	6/13	4/6
Candida infection	5/10	2/3
Aspergillus infection	1/2	1/2
Other organisms	0/1	1/1

Outcome by Risk

The randomization was stratified by risk of developing invasive fungal infections, *i.e.* high risk patients include those with allogeneic bone marrow transplants and relapsed leukemia and moderate risk patients include those with autologous transplants, newly diagnosed leukemia and other neoplasms. High risk patients had more prolonged neutropenia, both at baseline, and during treatment, presented in Table 7-48.

Table 7-48 Empirical Therapy Study (603/MSG42) – Duration of Neutropenia at Baseline and during Treatment – Modified Intention to Treat Population

Duration (days) Median	High Risk		Moderate Risk	
	Voriconazole (N = 143)	**Liposomal amphotericin B (N = 141)**	**Voriconazole (N = 272)**	**Liposomal amphotericin B (N = 281)**
Prior to randomization	10.5	8.7	7.4	7.3
During treatment*	5.7	5.7	4.4	4.7
Total*	17.8	17.2	13.1	12.3

*Derived from the Kaplan-Meier estimate.

Voriconazole success in the composite endpoint (31.5% vs. 29.8% in liposomal amphotericin B patients) was more pronounced in the high risk patients than in the moderate risk patients. Table 7-49 and Table 7-50 present these results.

Table 7-49 Empirical Therapy Study (603/MSG42) – Overall Response and Response by Component – High Risk Patients - Modified Intention to Treat Population

Response Parameters	Voriconazole (N=143) n/N (%)	Liposomal amphotericin B (N=141) n/N (%)	Point estimate (Raw) 95% CI
Overall response to empirical therapy	45/143 (31.5)	42/141 (29.8)	1.7 (-9.0, 12.4)
No breakthrough fungal infections within 7 days of End of Therapy	141/143 (98.6)	128/141 (90.8)	7.8 (2.7, 13.0)
Survival through 7 days of End of Therapy	131/143 (91.6)	128/141 (90.8)	0.8 (-5.8, 7.4)
No discontinuation due to toxicity or lack of efficacy before recovery from neutropenia	132/143 (92.3)	130/141 (92.2)	0.1 (-6.1, 6.3)
Resolution of fever during neutropenia	55/143 (38.5)	55/141 (39.0)	-0.6 (-11.9, 10.8)
Global response of baseline fungal infections at End of Therapy (Complete or partial response)	2/5	3/4	-35.0 (-95.4, 25.4)

Table 7-50 Empirical Therapy Study (603/MSG42) – Overall Response and Response by Component – Moderate Risk Patients - Modified Intention to Treat Population

Response Parameters	Voriconazole (N=272) n/N (%)	Liposomal amphotericin B (N=281) n/N (%)	Point estimate (Raw) 95% CI
Overall response to empirical therapy	63/272 (23.2)	87/281 (31.0)	-7.8 (-15.2, -0.4)
No breakthrough fungal infections within 7 days of End of Therapy	266/272 (97.8)	273/281 (97.2)	0.6 (-2.0, 3.3)
Survival through 7 days of End of Therapy	251/272 (92.3)	269/281 (95.7)	-3.5 (-7.4, 0.5)
No discontinuation due to toxicity or lack of efficacy before recovery from neutropenia	242/272 (89.0)	264/281 (94.0)	-5.0 (-9.6, -0.3)
Resolution of fever during neutropenia	80/272 (29.4)	99/281 (35.2)	-5.8 (-13.6, 2.0)
Global response of baseline fungal infections at End of Therapy (Complete or partial response)	4/8	1/2	0 (-77.5, 77.5)

Table 7-51 presents the frequency of breakthrough infections in high and moderate risk patients, as well as according to prior antifungal prophylaxis.

Table 7-51 Empirical Therapy Study (603/MSG42) - Breakthrough Infections by Risk and Prior Antifungal Prophylaxis – Modified Intention to Treat Population

Risk	Breakthrough Infections n/N (%)		
	Prior antifungal prophylaxis	**No prophylaxis**	**Total**
High Risk			
Voriconazole	1/83 (1.2)	1/60 (1.7)	2/143 (1.4)
Liposomal amphotericin B	9/99 (9.1)	4/42 (9.5)	13/141 (9.2)
Moderate Risk			
Voriconazole	1/139 (0.7)	5/133 (3.8)	6/272 (2.2)
Liposomal amphotericin B	4/151 (2.6)	4/130 (3.1)	8/281 (2.8)
Total			
Voriconazole	2/222 (0.9)	6/193 (3.1)	8/415 (1.9)
Liposomal amphotericin B	13/250 (5.2)	8/172 (4.7)	21/422 (5.0)

The effect of voriconazole in prevention of breakthrough fungal infections occurred predominately in high risk patients (2 voriconazole-treated patients *vs.* 13 liposomal amphotericin B-treated patients). Voriconazole-treated patients who had received prior antifungal prophylaxis also had fewer breakthrough infections (1 voriconazole-treated patient *vs.* 9 amphotericin B-treated patients).

7.2.1.8 Conclusions

In the Empirical Therapy Study (603), voriconazole did not fulfill the statistical criteria to show non-inferiority to liposomal amphotericin B as assessed by the composite endpoint. Voriconazole therapy prevented more breakthrough fungal infections, particularly due to *Aspergillus* species, dematiaceous filamentous fungi, and *Candida* species than did therapy with liposomal amphotericin B. The results of the Empirical Therapy Study (603), supported by the results of the efficacy in patients with documented fungal infections demonstrate that voriconazole may be considered an appropriate alternative to liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia, particular high risk patients with allogeneic bone marrow transplants, relapsed leukemia, and prolonged neutropenia**.**

7.3 Infections due to Emerging Pathogens

Appendix 4 presents information from a pooled analysis of efficacy in infections due to emerging fungal pathogens from across the voriconazole clinical program (except for the Global Comparative Aspergillosis Study [307/602], which was not available at the time of the original NDA submission). Information is presented on a total of 101 patients with documented non-*Aspergillus*, non-*Candida* fungal infections. Sixteen of these patients received voriconazole as primary therapy and 85 patients as salvage therapy. There were 35 patients with *Scedosporium* infections and 15 with *Fusarium* infections.

Among patients with *Scedosporium* infections, successful outcomes were observed in 16 of 27 patients (59.3%) with infections due to *Scedosporium apiospermum* and 2 of 8 patients with infections due to *Scedosporium prolificans.* Of these, 13 patients had documented central nervous system infections, seven of whom had successful outcomes following voriconazole therapy.

Among patients with Fusarium infections, 6 of 15 patients (40.0%) had successful outcomes, including patients with eye, sinus, and disseminated infections. Table 7-52 displays these results.

Table 7-52 Rare and Refractory Pooled Efficacy Analysis - Analysis of Outcome by Organism

Pathogen	Patients with Rare Pathogens (N=84)		Patients with Rare Pathogens as Part of a Mixed Fungal Infection (N=17)		Total Patients with Rare Pathogens* (N=101)
	Success with primary therapy	Success with salvage therapy	Success with primary therapy	Success with salvage therapy	Success with primary or salvage Therapy
	Success n/N				
*Scedosporium apiospermum***	1/1	14/25	0	1/1	16/27
Scedosporium prolificans#	0/2	2/4	0	0/2	2/8
Fusarium sp.	0	2/7	0	1/2	3/9
Fusarium solani	0/1	2/3	1/1	0/1	3/6

*Total: patients with rare and refractory infections alone or as part of a mixed fungal infection: number of patients less than number of isolates as each patient could have more than one species isolated
**Includes *P. boydii*
#Includes *S. inflatum*

Overall, the data support the efficacy of voriconazole for the treatment of patients with infections due to the emerging fungal pathogens, *Scedosporium* and *Fusarium*.

7.4 Candidiasis

The efficacy of voriconazole in candidiasis is supported by data from a double-blind comparative trial, the Esophageal Candidiasis Study (305), data from a planned interim analysis of a study of candidemia in non-neutropenic patients (608), as well as efficacy data gathered from the compassionate use program and from trials treating patients with infections unresponsive to other therapies or who were intolerant of other therapy, the Rare and Refractory Studies (309 and 604). Data from the pre-planned 10% interim analysis of the Global Comparative Candidemia Study (608) in non-neutropenic patients were included in the New Drug Application. To preserve the integrity of this critical trial, these data are not presented separately here.

7.4.1 Esophageal Candidiasis Study (305)

The Esophageal Candidiasis Study (305) was a randomized, double blind, double dummy, comparative multi-center trial comparing oral voriconazole and oral fluconazole for the treatment of esophageal candidiasis. This study was conducted predominantly in Europe from September 1995 to January 1999.

7.4.1.1 Study Objectives

The objectives of the study were to compare the efficacy, safety and tolerability of voriconazole and fluconazole in the treatment of *Candida* esophagitis in immunocompromised patients; and to compare the efficacy of voriconazole with that of fluconazole in concomitant oropharyngeal candidiasis, where present at study entry, in immunocompromised patients. Additional objectives were to examine the population pharmacokinetics of voriconazole and the susceptibility of fresh clinical isolates to both voriconazole and fluconazole in a large group of immunocompromised patients.

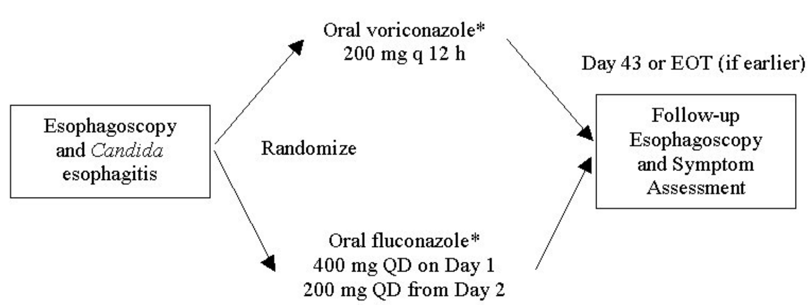
7.4.1.2 Study Design

This was a randomized, double blind, double dummy, comparative multi-center trial. Eligible patients were randomized to oral voriconazole tablets at a dose of 200mg bid or oral fluconazole capsules at a dose of 400 mg QD (once daily) on Day 1 and then 200mg QD from Day 2 onwards. Study treatment could be administered from two to six weeks. Efficacy and safety assessments were made during treatment, at End of Therapy, and four weeks after End of Therapy.

Esophageal candidiasis was confirmed by upper endoscopy with mycology/microbiology from specimens obtained during the procedure. Esophagoscopy was performed at screening and at Day 43 or the End of Therapy (if this was earlier). The extent of esophagitis was assessed using a protocol-specified grading system (0 to 4). Symptoms of esophageal candidiasis and symptoms and signs of oropharyngeal candidiasis were assessed according to protocol-specified criteria. Assessments of none, mild, moderate and severe were made for each sign and symptom during treatment and at End of Therapy and assessments of cured, improved, or failed were made for each sign and symptom at End of Therapy. At the four week follow-up, patients were assessed as: improvement, no change, relapse, or not evaluable. Mycological response was also assessed.

The study procedures are illustrated in Figure 7-14.

Figure 7-14 Esophageal Candidiasis Study (305) – Study Procedures



*Study treatment could be administered from two to six weeks.

7.4.1.3 Key Entry Criteria

Eligible patients included patients who were immunocompromised (e.g. by malignancy or its treatment, transplantation, or other conditions such as Human Immunodeficiency virus infection) and had a diagnosis of *Candida* esophagitis based on clinical symptoms at baseline (*e.g.* dysphagia, odynophagia, retrosternal pain), with or without oropharyngeal candidiasis. *Candida* esophagitis had to have been confirmed by esophagoscopy and a positive mycological culture from the brush or tissue biopsy. Patients were excluded who had evidence of systemic fungal infection, who had manifested oropharyngeal or esophageal candidiasis refractory to ≥200 mg/day of fluconazole within the six months prior to study entry, or who had received therapy with a systemic antifungal agent within the three days prior to baseline. Local oral therapy for candidiasis was prohibited during the study. Important exclusion criteria included: alanine transaminase, aspartate transaminase, or alkaline phosphatase above five times the upper limit of normal, serum creatinine > three times the upper limit of normal, life expectancy less than two months, and administration of excluded concomitant medications.

7.4.1.4 Statistical Methods

Efficacy Endpoints and Analyses

Primary Endpoint

The primary endpoint was esophageal response at end of treatment. The prospectively defined analysis of the primary endpoint entailed the construction of an unstratified 95% confidence interval for the difference in the esophageal success rate between treatments in the Per Protocol and Intention to Treat populations. An analysis stratified for country was also performed. The stratified confidence interval was derived from a method of linear stratification that weighted according to the reciprocal of the variance. The confidence interval was compared with a non-inferiority margin of –15%. In the Intention to Treat population the symptomatic assessment of esophageal candidiasis was substituted where the end of Therapy esophagoscopy assessment was missing. *Post-hoc* sensitivity analyses around the primary endpoint were performed.

Analysis Populations

The primary analysis populations were Intention to Treat and Per Protocol. The definitions of the two populations are given in Table 7-53.

Table 7-53 Esophageal Candidiasis Study (305) – Analysis Populations

Population	Criteria
Intention to Treat	• All patients who received at least one dose of randomized study drug.
Per Protocol	• All patients who received at least one dose of randomized study drug • Had no significant deviation from the inclusion/exclusion criteria and planned study conduct • Had endoscopically confirmed *Candida* esophagitis • Received at least 12 days of study treatment • Had an End of Therapy evaluation including a repeat esophagoscopy • Had evidence of adequate adherence to therapy • Had visits at each assessment within the ± five day window • Had received specified antifungal or other prohibited medication prior to baseline or during the study • Had no evidence of oral or esophageal candidiasis within the six months prior to study entry which had failed to respond clinically and mycologically to ≥200 mg/day fluconazole • Had not received Granulocyte Colony Stimulating Factor, Granulocyte Macrophage Colony Stimulating Factor or white blood cell transfusions for the treatment of the fungal infection.

Sample Size Determination

The sample size was based upon the following: a non-inferiority criterion which required that the lower bound of the 95% confidence interval around the difference in success rates was greater than -15%; an expected success rate of 80% in both treatment groups; an expected 30% of the patients enrolled would be excluded from the Per Protocol population; and the study would have 80% power to show non-inferiority at the two-sided level of significance. Therefore the study was designed to enroll a total of 320 patients (160 per treatment group).

During the study, a blinded evaluability assessment suggested that approximately 370 patients would need to be treated in order to accrue the required number of eligible patients. It was agreed that the study should continue to recruit to the limit of the available drug supplies, therefore 391 patients were randomized.

Randomization and Stratification

Patients were randomized in a 1:1 ratio to receive either voriconazole or fluconazole (in a double-dummy fashion). The randomization was not stratified.

Statistical Analysis Plan

The statistical analysis plan was finalized 19 August 1999, prior to database release. Generic Protocol Amendment IV (October 1998) amended the planned sample size from 320 to 400 patients, as discussed in the sample size section. No other protocol amendments directly affected the statistical analyses.

Interim Analyses

One pre-planned blinded interim analysis of efficacy was performed after 100 patients had completed the study. The purpose of the analysis was to aid the planning of the voriconazole clinical development program. The treatment code blind was to be broken only if the success rate in one group was <60% and more than 25% worse than the other group. The interim analysis was not governed by any formal stopping rule and as stated in the protocol, no adjustment to the final analysis was made as a result of this interim. Although there was no statistical testing in the interim analysis, 95% confidence intervals were produced to assess the difference in success rates. If the difference in success rates was deemed unethically large, then the early termination of the trial was to be considered.

The results of the blinded interim analysis suggested that symptomatic and mycological response rates were similar between the treatment groups. The interim analysis was performed by a statistician uninvolved in the study and the blinded results were disseminated to the clinical project team leader and the biometrics project team leader. The results were subsequently unblinded and passed to senior management. No one directly involved in management of the trial accessed the blinded or unblinded interim results until the final statistical analyses were performed.

7.4.1.5 Protocol Amendments

Protocol amendments, implemented after study initiation that affected entry criteria, efficacy or safety assessments included the following, which were instituted in July 1996:

- The upper age limit of 70 years was removed.
- Permitted the routine use of hematopoietic growth factors (*e.g.* Granulocyte Colony Stimulating Factor) in the treatment of hematologic diseases or coadminsitration with cytotoxic chemotherapy as long as such treatments were not started during therapy for the disease under study.
- Exclusion criteria for liver function test abnormalities were changed from two to three times the upper limit of normal to five times the upper limit of normal.
- Esophagoscopy results conducted within 96 hours of study entry did not have to be repeated at baseline.

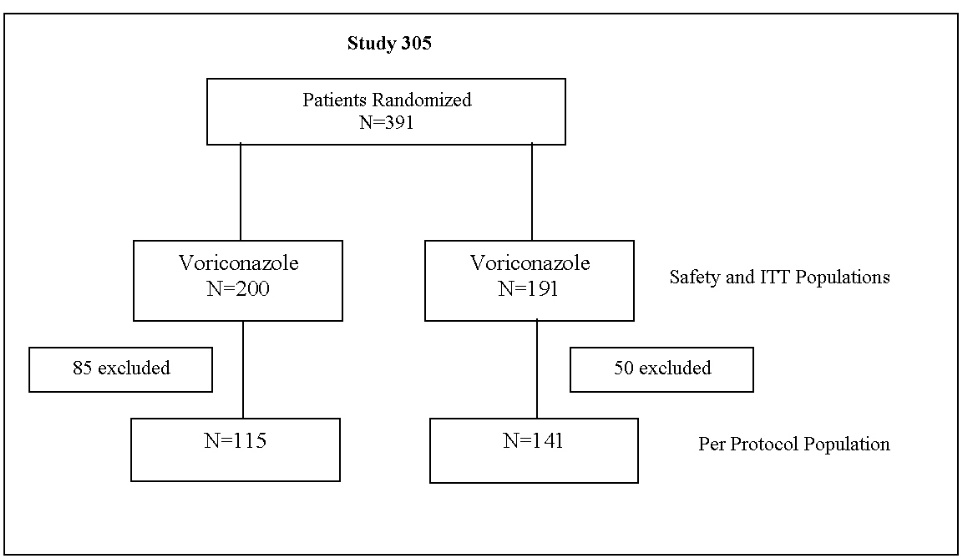
In June 1998 a blinded assessment of evaluability was performed for patients on the database with clinical signs and symptoms data. As a result of this assessment it was estimated that approximately 370 patients would need to be enrolled to accrue 224 evaluable patients. A protocol amendment, which was finalized on 30 October 1998, explained that the number of patients required to be randomized was increased to 400 because the number of evaluable patients recruited was less than originally anticipated. The amendment stated that the assumption that 224 evaluable patients would represent 70% of all enrolled patients was incorrect, given the overall evaluability rate of 56%. Consistent with this, in July 1998 a decision had been made that recruitment into the study should continue to the limit of drug supplies available at that time.

7.4.1.6 Results

Patient Disposition

The disposition of enrolled patients is summarized in Figure 7-15.

Figure 7-15 Esophageal Candidiasis Study (305) - Evaluation Groups



The reasons for exclusion from the Per Protocol population, including the number of patients excluded due to premature discontinuation of study drug are shown in Table 7-54.

Table 7-54 Esophageal Candidiasis Study (305) - Reasons for Exclusion from Per Protocol Analysis

Per Protocol Population Reason for Exclusion*	**Voriconazole Intention to Treat Population (N=200) Number excluded from population**	**Fluconazole Intention to Treat Population (N=191) Number excluded from population**
No evidence of esophageal candidiasis at baseline	29	15
Received systemic antifungal medication less than three days prior to baseline, or forbidden medication prior to baseline	4	2
Received forbidden medication during study (including fluconazole)	13	12
Less than 12 days of study therapy	30	9
Withdrew from study	7	1
AE possibly related to study drug	6	1
AE not related to study drug	5	2
Discontinued due to a laboratory abnormality	2	1
Died	3	2
Protocol violation	4	1
Lost to follow-up	3	1
Missing End of Therapy esophagoscopy	7	10
No End of Therapy symptomatic assessment	1	0
Other	1	2
Total	85	50

AE = adverse event
*Patients were assigned one reason for exclusion according to a Sponsor-defined hierarchy and are counted only once in this table, although they may have had more than one reason for exclusion.

The imbalance in numbers of patients without evidence of baseline esophageal candidiasis was the chance result of the randomization. There was no center effect detected when sought. There were 21 more voriconazole patients than fluconazole patients excluded because of early discontinuation (less than 12 days of study medication).

Baseline Characteristics/Demographics

The demographic characteristics of enrolled patients were similar, as shown in Table 7-55.

Table 7-55 Esophageal Candidiasis Study (305) – Demographic Characteristics - Intention to Treat Population

	Voriconazole (N = 200)			Fluconazole (N = 191)		
	Males (N = 153)	**Females (N = 47)**	**Total (N = 200)**	**Males (N= 144)**	**Females (N = 47)**	**Total (N = 191)**
Age range (years) Mean	22 – 75 37.7	19 – 52 32.3	19 – 75 36.4	23 – 71 38.3	19 – 71 34.9	19 – 71 37.4
Weight range (kg) Mean	35.0 – 97.0 61.8	34.0 – 135.0 54.7	34.0 – 135.0 60.1	34.0 – 85.0 59.8	36.0 – 80.0 52.2	34.0 – 85.0 57.9
Race						
White	116 (75.8)	19 (40.4)	135 (67.5)	106 (73.6)	19 (40.4)	125 (65.4)
Black	23 (15.0)	25 (53.2)	48 (24.0)	25 (17.4)	25 (53.3)	50 (26.2)
Asian	11 (7.2)	2 (4.3)	13 (6.5)	11 (7.6)	2 (4.3)	13 (6.8)
Other	3 (2.0)	1 (2.1)	4 (2.0)	2 (1.4)	1 (2.1)	3 (1.6)

The baseline characteristics of enrolled patients are summarized in Table 7-56.

Table 7-56 Esophageal Candidiasis Study (305) – Baseline Characteristics – Intention to Treat Population

	Voriconazole (N=200) n (%)	**Fluconazole (N=191) n (%)**
Primary Diagnosis		
Esophageal candidiasis	200 (100.0)	191 (100.0)
Secondary Diagnosis		
Oropharyngeal candidiasis	168 (84.0)	157 (82.2)
Prior Antifungal Therapy*		
Antifungal Drugs	50 (25.0)	46 (24.1)
Imidazoles	4 (2.0)	3 (1.6)
Polyenes	46 (23.0)	42 (22.0)
Triazoles	1 (0.5)	1 (0.5)
CD4 Cell Count **		
CD4 $\geq$ 200 cells/mm^3	23 (11.5)	23 (12.0)
CD4 < 200, > 50 cells/mm^3	43 (21.5)	43 (22.5)
CD4 $\leq$ 50 cells/mm^3	117 (58.5)	114 (59.7)
CD4 cell count not available	7 (3.5)	0
Mycology of Primary Diagnosis#		
Candida albicans	179 (89.5)	175 (91.6)
Candida glabrata	6 (3.0)	6 (3.1)
Candida krusei	2 (1.0)	2 (1.1)
Candida parapsilosis	0	1 (0.5)
Candida tropicalis	0	1 (0.5)
Candida spp.	14 (7.0)	6 (3.1)
Penicillium marneffei	0	1 (0.5)

*Previous antifungal drug treatment for primary and/or secondary diagnosis in the three days prior to receipt of study drug
**Classification: non-AIDS = CD4 cell count ≥200 cells/mm^3, AIDS = CD4 cell count > 50 - < 200 cells/mm^3; advanced AIDS = CD4 cell count ≤50 cells/mm^3
#The denominator used to calculate the percent of patients is the number of patients in each treatment arm

In the voriconazole group, 153 patients (76.5%) had HIV infection present at baseline and in the fluconazole group 145 patients (75.9%) had HIV infection. In addition, 34 voriconazole patients (17.0%) and 33 fluconazole patients (17.3%) had positive serological/virological findings for HIV infection.

Duration of Therapy

Duration of therapy is summarized in Table 7-57.

Table 7-57 Esophageal Candidiasis Study (305) – Duration of Therapy (Elapsed Time) – Intention to Treat Population

	Duration of Therapy (days)*	
	Voriconazole (N=200)	Fluconazole (N=191)
Median (range)	14 (1 – 45)	15 (2 – 49)

*Elapsed time

Efficacy Evaluation

Table 7-58 shows Per Protocol and Intention to Treat population efficacy data, where success is defined as 'cured' or 'improved'.

Table 7-58 Esophageal Candidiasis Study (305) – Primary Efficacy Analyses – Per Protocol and Intention to Treat Populations

Efficacy endpoint	Population	Voriconazole	Fluconazole	Difference (voriconazole - fluconazole)	95% CI[a] for Difference
Esophageal success[b] (Esophagoscopy)	Per Protocol	98.26% (n=115)	95.04% (n=141)	3.23%	(-1.08%, 7.53%)
Esophageal success (esophagoscopy +symptoms)	Intention to Treat	87.50% (n=200)	89.53% (n=191)	-2.03%	(-8.34%, 4.29%)
Esophageal success (symptoms)	Intention to Treat	88.00% (n=200)	91.10% (n=191)	-3.10%	(-9.15%, 2.95%)

Success = cured + improved
[a]CI = Unstratified 95% confidence interval: Lower limit to be compared to non-inferiority margin of –15%:
[b]Primary analysis

Based on the results from the primary analysis (Per Protocol population), voriconazole met the criterion of non-inferiority compared with fluconazole in the treatment of esophageal candidiasis since the lower limit of the 95% confidence interval was greater than –15%. The median time to cure for both groups was eight days.

All primary, secondary and stratified primary analyses met the criterion for non-inferiority (lower end of the 95% confidence interval no lower than –15%). However in one of the sensitivity analyses of the primary endpoint, the lower end of the 95% confidence interval for the secondary analysis (stratified for country) was –16.39%. This analysis was extremely conservative because any symptomatic assessment was disregarded, even in the case of clear clinical success, and all those without End of Therapy upper endoscopy were set to 'failed'.

At four week follow-up, 10 of 176 voriconazole patients (5.7%) and 18 of 174 fluconazole patients (10.3%) had symptoms consistent with relapse. There was no evidence to suggest a positive correlation between the isolate voriconazole MIC and either clinical response or global outcome.

The results of the population pharmacokinetic analyses are included in the overall pharmacokinetic/pharmacodynamic analysis (Sec. 6) of this Briefing Document.

Mycological *in vitro* assessment was performed on samples from patients in the Esophageal Candidiasis Study (305). Table 7-59 shows MIC_{50} and MIC_{90} values determined for the clinical isolates from this study.

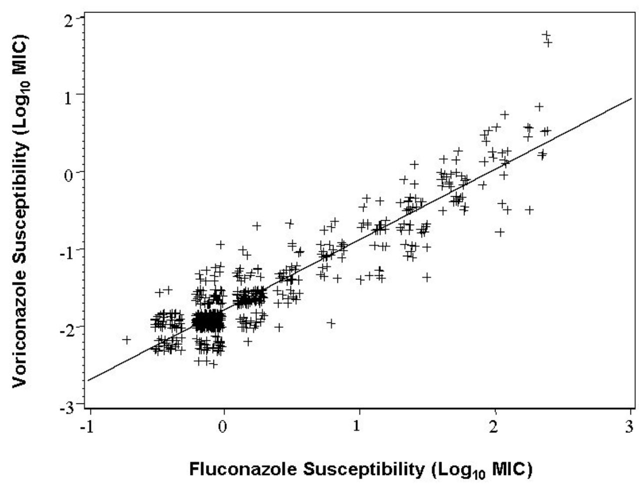
Table 7-59 Esophageal Candidiasis Study (305) – *Candida* MICs*

Organism	Number of Isolates	Antifungal Agent	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
C .albicans	546	Voriconazole	0.003 - > 25	0.012	0.098
		Fluconazole	0.19 - > 100	0.78	12.5
		Itraconazole	< 0.0015 - > 25	0.006	0.049
		Amphotericin B	0.003 – 0.78	0.098	0.39
C. glabrata	56	Voriconazole	0.012 - >25	0.19	3.1
		Fluconazole	1.56 - > 100	12.5	100
		Itraconazole	0.012 - > 25	0.19	6.3
		Amphotericin B	0.049 – 0.39	0.098	0.19
C. krusei	17	Voriconazole	0.049 – 0.39	0.098	0.39
		Fluconazole	12.5 – 50	25	50
		Itraconazole	0.003 – 0.098	0.006	0.098
		Amphotericin B	0.024 – 0.78	0.049	0.19
C .parapsilosis	5	Voriconazole	0.006 – 6.3		
		Fluconazole	0.78 - > 100		
		Itraconazole	0.003 - > 25		
		Amphotericin B	0.006 – 0.19		
C. tropicalis	7	Voriconazole	0.006 – 0.049	0.024	0.049
		Fluconazole	0.39 – 1.56	0.39	1.56
		Itraconazole	0.003 – 0.006	0.006	0.006
		Amphotericin B	0.012 – 0.39	0.049	0.39

*NCCLS M27A Method (NCCLS 1997, Rex *et. al.* 1997)

Table 5-3 shows the NCCLS interpretive guidelines for susceptibility testing *in vitro* of *Candida* species (NCCLS, 1997). Voriconazole MICs for the 631 clinical *Candida* isolates are linearly related to that for fluconazole, however, shifted by approximately 1.8 logs as shown in Figure 7-16.

Figure 7-16 Esophageal Candidiasis Study (305) - Relationship between Voriconazole and Fluconazole Minimum Inhibitory Concentration of Clinical Isolates



7.4.1.7 Conclusions

In the Esophageal Candidiasis Study (305), a large randomized double-blind study, voriconazole was shown to be not inferior to fluconazole in successfully treating biopsy- and mycologically-proven cases of esophageal candidiasis. This included a subset of patients with severe esophagitis at baseline. Overall, voriconazole produced endoscopically-proven success and clinically successful outcomes in 87.5% and 88.0% of the Intention to Treat population patients, respectively. The results of this study provided evidence of efficacy in *Candida* infections prior to pursuing the study of voriconazole in the treatment of more invasive *Candida* infections, the Global Comparative Candidemia protocol (608).

7.4.2 Summary of Voriconazole Treatment of Infections due to *Candida* Infections

The results of the Esophageal Candidiasis Study (305) provided evidence of efficacy in *Candida* infections prior to pursuing the study of voriconazole in the treatment of more invasive *Candida* infections. The Global Comparative Candidemia protocol (608) is an evaluation of voriconazole compared to conventional amphotericin B followed by fluconazole in the treatment of candidemia in non-neutropenic patients. This study protocol was submitted in Feb. 1998 and is ongoing, with over half of the targeted patients (426) enrolled to date.

Appendix 4 presents information from a pooled analysis across the voriconazole clinical program on a total of 91 patients with documented serious systemic *Candida* infection. This includes 43 patients who received voriconazole as salvage therapy, 36 of whom were classified as previous efficacy failures after treatment with one or more previous antifungal agents. Success was seen in 22 of 43 patients (51.2%).

Together with the demonstrated *in vitro* potency and *in vivo* efficacy, these data support the use of voriconazole in patients with serious *Candida* infections.

8 CLINICAL SAFETY

8.1 Introduction

The safety of voriconazole has been assessed in a clinical development program incorporating healthy volunteers, patients with fungal infections and immunocompromised patients with persistent fever and neutropenia receiving voriconazole for the empirical treatment of fungal infections.

The Integrated Summary of Safety in the November 2000 New Drug Application (NDA) for voriconazole presented integrated safety data from 2772 healthy volunteers and patients enrolled in 28 Phase 1, 2, and 3 studies conducted by Pfizer Global Research and Development (PGRD). An update of the Integrated Summary of Safety completed in June 2001 enlarged the safety database to a total of 3267 healthy volunteers and patients.

Pfizer uses two systems to collect and evaluate safety data. Deaths and serious adverse events are collected and maintained in Pfizer's Adverse Event Monitoring (AEM) database. These events are reported from the AEM database. Other adverse events are reported from the project database. The AEM database is continually updated and may contain more current information than the project database. In this safety section, serious adverse events and deaths from two additional therapeutic and three additional clinical pharmacology studies are included, as they are included in the more current AEM database. Serious adverse events and deaths reported from the AEM database include all events occurring up to 30 days following the end of therapy.

In the following discussion of discontinuations, adverse events, and laboratory abnormalities (*i.e.* sections other than discussions of serious adverse events and deaths), the Sponsor has used a treatment emergent algorithm and presented All Causality events, except as otherwise noted. All summary tables in this section report adverse events using coded terms based on standard coding dictionaries.

8.2 Organization of the Safety Section

This safety section discusses data as follows:

1. Clinical Pharmacology Studies (Section 8.5): Discussion of the most common discontinuations due to adverse events, deaths and serious adverse events, treatment emergent adverse events and laboratory abnormalities in Phase 1 pharmacokinetic and tolerability studies in healthy volunteers.

2. Comparative Phase 3 Studies (Section 8.6): Discussion of the most discontinuations due to adverse events, deaths and serious adverse events, treatment emergent adverse events, visual function tests and laboratory abnormalities in the three large comparative Phase 3 studies described in Table 8-1.

3. Pooled Safety Databases (Section 8.7): Discussion of discontinuations due to adverse events, deaths and serious adverse events, treatment emergent adverse events and laboratory abnormalities in the pooled safety databases described in Table 8-1. This section includes discussions of long term safety and safety in pediatric patients (aged two to <12 years) as well.

4. Detailed discussion of specific safety considerations (Section 8.8): Using data from the first three populations, as well as other datasets, as appropriate, this section discusses the clinical and relevant nonclinical data for several selected safety issues. Included are: visual disturbances, hepatic function, skin reactions, cardiac function, sepsis and host resistance, renal function and hallucinations.

8.3 Description of the Pooled Databases

The discussions of safety focus on:

(1) A pooled population of healthy volunteers from 24 of 58 studies in the clinical pharmacology program. As described in more detail in Section 8.5, this group does not include subjects involved in drug interaction studies and special populations of subjects.

(2) Three large, comparative Phase 3 studies

The Global Comparative Aspergillosis Study (307/602): In this randomized, open label study, voriconazole is compared with conventional amphotericin B followed by Other Licensed Antifungal Therapy in patients who were being treated for invasive aspergillosis and who required initial intravenous therapy.

The Empirical Therapy Study (603): In this randomized, open-label study, voriconazole is compared with liposomal amphotericin B in patients with persistent fever and neutropenia and who required intravenous medication, generally for a short period of treatment.

The Esophageal Candidiasis Study (305): In this randomized, double-blind double-dummy study, voriconazole is compared with fluconazole in patients with esophageal candidiasis, who were immunocompromised, although otherwise ambulatory and able to take oral medication

Within each discussion of these studies, the Safety or Intention to Treat population (where identical) is the population used for the safety analyses.

(3) Pooled safety databases including the following subgroups:

- Therapeutic Studies This subgroup includes eight Phase 3 studies: three active-controlled treatment studies (Studies 305, 307/602, and 608), one active-controlled empirical therapy trial (Study 603), and four non-comparative treatment studies (Studies 303, 304, 309, and 604). Data from Studies 608, 309 and 604 are interim, with a cut-off for inclusion of safety data in this briefing document of 1 May 2001.
- Compassionate Use This subgroup includes patients entered into compassionate use studies and extension studies following therapeutic studies (Studies 301, 303A, 304A, 311, 312, 606, 607)
- Overall Pooled This group includes the Therapeutic Studies subgroup and the Compassionate Use Studies subgroup. It should be noted that individual patients may be included in both of these populations if they were treated in a study included in the Therapeutic Studies group, then continued treatment with voriconazole in an extension or compassionate use study. Therefore, a total of 145 voriconazole-treated patients are counted more than once in the Overall Pooled population.

- Non-Therapeutic Studies This group includes a Phase 1 trial in patients, the Multiple Dose Adult Patient Pharmacokinetic Study (673) and an early Phase 2 dose ranging study, the Dose Ranging Oropharyngeal Candidiasis Study (302). Considering the atypical nature of treatment in these two studies, they have not been included in the overall pooled database and are discussed separately.

Of the pooled databases, the Therapeutic Studies subgroup includes patients most representative of the range of underlying conditions and diseases where voriconazole will be most commonly used at the recommended doses.

Table 8-1 summarizes the populations used for the safety presentations.

Table 8-1 Number of Patients and Volunteers in Studies Included in the Safety Subgroups

Group	Voriconazole	Comparator*
Clinical pharmacology Studies	N = 443	Placebo N = 135
Phase 3 Comparative Studies*		
Esophageal Candidiasis Study (305)	N = 200	Fluconazole N = 191
Empirical Therapy Study (603)	N = 421	Liposomal amphotericin B N = 428
Global Comparative Aspergillosis Study (307/602)	N = 196	Amphotericin B (+ Other Licensed Antifungal Therapy) N = 185
Single Dose Pediatric Study (249)	N = 11	
Multiple Dose Pediatric Study (1007)	N = 28	
Pooled Safety Databases July 2001		
Therapeutic Studies#	N = 1493	N = 856 Amphotericin B formulations N = 665 Fluconazole N = 191
Compassionate Use	N = 597##	N/A
Overall Pooled**,#	N = 2090**	N = 856 Amphotericin B formulations N = 665 Fluconazole N = 191
Non-Therapeutic Studies	N = 185	Fluconazole N = 6
Pooled Safety Databases Nov. 2000 NDA		
NDA Therapeutic Studies	N = 1214	
NDA All Voriconazole	N = 1946	
NDA Long-Term Therapy	N = 304	
Pediatric	N = 52	

N/A = not applicable
*The safety populations presented in this section include the Intention to Treat population for Study 305 and the Safety populations for Studies 307/602 and 603.
**This total includes 145 patients who were previously treated in clinical studies.
#It should be noted that the serious adverse events and deaths tables include 4 serious adverse events and 2 deaths from two studies, Japanese Non-Comparative Deep-Seated Mycoses Study (1001) and the Comparative Paracoccidioides Study (1010). Patients from these studies are not included in the denominators for these tables. Data from these studies are not included in any other safety tables.
##Includes 3 patients treated with compassionate use outside of formal protocols.

8.4 Nature of the Patient Populations in the Phase 3 Comparative Studies

Patients treated with voriconazole generally are seriously ill and immunocompromised. In the Esophageal Candidiasis Study (305), 370/391 (94.6%) of patients had human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) as an underlying condition. In the Empirical Therapy Study (603) and the Global Comparative Aspergillosis Study (307/602), a large number of patients had underlying hematological disease or malignancy and many had received a bone marrow or peripheral stem cell transplant, as presented in Table 8-2:

Table 8-2 Global Comparative Aspergillosis Study (307/602) and Empirical Therapy Study (603) – Number and Percent of Patients with Bone Marrow Transplantation – Safety and Intention to Treat Populations

Transplant type	Global Comparative Aspergillosis Study (307/602) (N = 379)* n (%)	Empirical Therapy Study (603) (N = 849) n (%)**
Allogeneic bone marrow transplant	55 (14.5)	85 (10.0)
Allogeneic peripheral stem cell transplant	27 (7.1)	73 (8.6)
Autologous bone marrow transplant	6 (1.6)	28 (3.3)
Autologous peripheral stem cell transplant	14 (3.7)	237 (27.9)
No bone marrow or stem cell transplant	277 (73.1)	426 (50.2)

*Intention to Treat population
**Safety population

Because of these serious underlying conditions, the patients studied in the voriconazole program also received numerous concomitant medications, either for their underlying disease or intercurrent illness. Table 8-3 summarizes concomitant medication use in the comparative studies:

Table 8-3 Phase 3 Comparative Studies - Concomitant Medication Use

	Esophageal Candidiasis (305)		Empirical Therapy Study (603)		Global Comparative Aspergillosis Study (307/602)	
	Voric. (N = 200)	Fluconazole (N = 191)	Voric. (N = 421)	L-AMB (N = 428)	Voric. (N = 196)	Amphotericin B (N = 185)
Number of patients receiving concomitant medications	195 (98%)	187 (98%)	421 (100%)	428 (100%)	196 (100%)	185 (100%)
Total number of concomitant medications	1,596	1,444	9,843	10,251	5,115	3,877
Mean number of concomitant medications/ patient	8.0	7.6	23.4	24.0	26.1	21.0

L-AMB = liposomal amphotericin B; Voric. = voriconazole

In reviewing the safety profile of voriconazole, the nature of the patient population must be considered. Patients who received voriconazole were seriously ill and received numerous concomitant medications. As a result, the discussion of voriconazole safety in this document focuses on data from randomized comparative trials and tolerability in the healthy Phase 1 population, in addition to the overall population. The following section describes the organization of the safety information in this document.

8.5 Safety Assessment in Clinical Pharmacology Studies

A description of the subjects included in this population is given in Section 8.1 and Table 8-1. In total, 1150 subjects received voriconazole, placebo, or comparator agent in the voriconazole clinical pharmacology program. As described in Section 8.1, the pooled Clinical Pharmacology Studies safety population excludes subjects dosed in 34 drug interaction studies and various special populations. Table 8-4 presents the disposition of patients in the clinical pharmacology program.

Table 8-4 Disposition of Subjects in the Clinical Pharmacology Program

Group	Overall number of subjects	Subjects receiving voriconazole	Subjects receiving placebo [a]
Total*	1150	986	166
Pooled subjects [b]	509	443	135
Special population Patients [c]	150	144	0
Special population Japanese	80	71	12
Subjects in Interaction studies	365	310	0
Subjects in SBECD studies [d]	46	18	19

[a]Includes subjects receiving placebo and voriconazole in crossover studies.
[b]Primary healthy volunteer pooled safety population.
[c]Includes subjects with hepatic and renal impairment, and children and adults with hematological malignancy in PK studies.
[d]Primarily investigated the safety and PK of vehicle (sulfobutylether-beta-cyclodextrin; SBECD).
*Serious adverse events and deaths discussion includes additional studies: Suspension Bioequivalence Study (1019), Single Dose Comparative QTc Study #1 (1021), Single and Multiple Oral Dose Study in Japan (1022)

The pooled population includes 443 voriconazole-treated subjects and 135 placebo-treated subjects. With the exception of the Male/Female and Young/Elderly Study (250), where gender and age effects were investigated, and 36 females and 18 elderly males were included, all subjects were healthy, young male volunteers. Treatment durations were up to 14 days for intravenous and 29 days for oral voriconazole. Of the 443 voriconazole-treated subjects, 368 received oral and 167 received the intravenous formulation of voriconazole. Some subjects were involved in switch studies and received both intravenous and oral voriconazole.

8.5.1 Discontinuations due to Adverse Events

Discontinuations due to adverse events in Phase 1 were similar between voriconazole (14/443; 3.2%) and placebo (3/135; 2.2%). Two volunteers in the voriconazole group and one in the placebo group discontinued due to abnormal liver function tests (LFTs) and three volunteers discontinued with abnormal vision in the voriconazole group (3/443; 0.7%).

8.5.2 Deaths and Serious Adverse Events

There were no deaths in the subjects included in the Clinical Pharmacology Studies pooled safety population. There were two serious adverse events, possible epileptic seizure (placebo, n=1) and appendicitis (voriconazole, n=1). Neither was considered related to treatment.

Serious adverse events in the pediatric clinical pharmacology studies (Single Dose Pediatric Study [249] and Multiple Dose Pediatric Study [1007]) are discussed in Section 8.7.3. In the other studies not included in the pooled population, there were seven other serious adverse events. These serious adverse events are summarized in Table 8-5.

Table 8-5 Serious Adverse Events Occurring on Therapy or Within 30 Days of End of Therapy in Studies Not Included in the Clinical Pharmacology Studies Pooled Population

Study	Event Term (s)	Treatment Group	Onset of Event (Day of Treatment)	Causality	Action Taken	Outcome
Voriconazole on Indinavir Interaction Study (244)	Sebaceous cyst	Indinavir/ placebo	2	Other illness	Drug discontinued Day 5	Resolved
Hemodialysis Study (1011)	Mental confusion, visual hallucination, chest pain, weakness, decreased blood pressure, mild slurring of speech, clotted dialysis access device, altered gait	Voriconazole	2	Study drug	Drug discontinued Day 2	Resolved
Multiple Dose Renal Impairment Study (1016)	Elevated creatinine	Voriconazole	6	Study drug	Drug discontinued Day 6	Resolved
Suspension Bioequivalence Study (1019)	Ventricular ectopics	Voriconazole	7	Study drug	Drug discontinued Day 7	Resolved
Single Dose Comparative QTc Study #1 (1021)	Anaphylactoid reaction	Placebo/ voriconazole	8	Infusion	Drug discontinued Day 8	Resolved
Single Dose Comparative QTc Study #1 (1021)	Anaphylactoid reaction	Voriconazole	8	Infusion	Drug discontnued Day 8	Resolved
Single and Multiple Oral Dose Study in Japan (1022)	Fever, vomiting, nausea, diarrhea, rigors	Voriconazole	13 (post therapy event)	Study Drug	Post therapy event	Resolved

Of these events, the two cases of anaphylactoid reaction merit more discussion. These events involved two female volunteers in the Single Dose Comparative QTc Study #1. The first had symptoms of faintness, nausea and pruritus of the face, ears and legs, approximately one minute following initiation of voriconazole intravenous infusion. She became hot, diaphoretic and tachycardic and the intravenous infusion was stopped three minutes after its initiation. All symptoms resolved 20 minutes after the symptoms had begun. The second subject received intravenous placebo (SBECD) infusion and two minutes after initiation of the infusion she complained of feeling distant, tightness of the chest and epigastric discomfort. She became hot, diaphoretic and developed an erythematous rash on her chest and left arm. The infusion was discontinued four minutes after it had begun and the event subsequently resolved. Both cases of anaphylactoid reaction were considered by the investigator to be serious and related to the intravenous infusion.

The Single Dose Comparative QTc Study #1 (1021) was stopped as a consequence of the two serious adverse events and a second study of identical design (Single Dose Comparative QTc Study #2 [1027]) was initiated. In this study, 2 more cases of anaphylactoid reaction occurred within a few minutes of initiation of the voriconazole intravenous infusion. These two events were not considered to be serious by the investigator, but the study was again stopped as a consequence.

8.5.3 Treatment Emergent Adverse Events

The 10 most frequent all causality adverse events in all voriconazole subjects are summarized in Table 8-6:

Table 8-6 Most Frequently Reported Adverse Events - Clinical Pharmacology Studies

Event	All voriconazole subjects (N = 443) n (%)	PO voriconazole (N = 368) n (%)	IV voriconazole (N = 167) n (%)	Placebo (N = 135) n (%)
Abnormal vision	154 (34.8)	127 (34.5)	46 (27.5)	16 (11.9)
Headache	134 (30.2)	108 (29.3)	34 (20.4)	27 (20.0)
Photophobia	74 (16.7)	60 (16.3)	32 (19.2)	4 (3.0)
Dizziness	32 (7.2)	28 (7.6)	4 (2.4)	9 (6.7)
Abdominal pain	25 (5.6)	20 (5.4)	5 (3.0)	4 (3.0)
Asthenia	24 (5.4)	21 (5.7)	3 (1.8)	1 (0.7)
Nausea	23 (5.2)	19 (5.2)	5 (3.0)	3 (2.2)
Respiratory tract infection	17 (3.8)	15 (4.1)	2 (1.2)	5 (3.7)
Eye pain	19 (4.3)	17 (4.6)	2 (1.2)	4 (3.0)
Application site infection/inflammation	16 (3.6)	2 (0.5)	14 (8.4)	1 (0.7)

The most frequently observed adverse events were related to visual disturbances (abnormal vision, photophobia), headache and dizziness. The nature and consequence of visual disturbances are discussed in 8.8.1. Headache was more frequent in voriconazole treated patients. The frequency of dizziness was similar to that observed in placebo-treated patients.

Asthenia and application site infection/inflammation were noticeably reported more frequently in the voriconazole compared with the placebo group. Asthenia was not reported as a severe adverse event and did not result in discontinuation in any subject. Application site infection/inflammation included reports of inflammation or phlebitis/thrombophlebitis at the cannula/infusion site. This type of reaction was not reported as severe and did not result in discontinuation.

8.5.4 Laboratory Abnormalities

Overall the rate of laboratory abnormalities was low in both voriconazole and placebo groups and there were no abnormalities of hematology parameters. The rates of renal and hepatic laboratory abnormalities are summarized in Table 8-7.

Table 8-7 Clinically Significant Renal and Hepatic Laboratory Abnormalities – Clinical Pharmacology Studies

Laboratory Parameter	Units	Criterion	Voriconazole n/N (%)	Placebo n/N (%)
Liver function				
Total bilirubin	mg/dL	>1.5 x ULN	2/431 (0.5)	2/127 (1.6)
AST	IU/L	>3.0 x ULN	4/431 (0.9)	1/127 (0.8)
ALT	IU/L	>3.0 x ULN	5/431 (1.2)	0
Alkaline Phosphatase	IU/L	>3.0 x ULN	0	0
Renal function				
Creatinine	mg/dL	>1.3 x ULN	0	0
Urea	mg/dL	>1.3 x ULN	1/430 (0.2)	0

ALT = alanine transaminase; AST = aspartate transaminase; ULN - Upper Limit of Normal

Abnormalities in liver function tests were infrequent and were reversible after discontinuation. No abnormalities of serum creatinine were observed.

8.5.5 Conclusions

The safety assessment of clinical pharmacology studies with voriconazole given by both oral and intravenous routes shows that adverse events were infrequently reported and infrequently resulted in discontinuation. In particular, abnormal vision, although occurring at a rate of approximately 35%, was rarely considered severe and resulted in discontinuation in only three cases in the pooled Clinical Pharmacology studies population. Changes in laboratory parameters were infrequently observed in the healthy population.

8.6 Safety Assessment in Phase 3 Comparative Trials

8.6.1 Global Comparative Aspergillosis Study (307/602)

In the randomized open label Global Comparative Aspergillosis Study (307/602), immunosuppressed patients with acute invasive aspergillosis were randomized to receive either voriconazole or amphotericin B. Initial treatment with the intravenous formulation of voriconazole was to be given for at least seven days, and could be followed by oral voriconazole for up to 12 weeks (although therapy could be extended to 16 weeks). Patients randomized to amphotericin B were to maintain therapy for at least 14 days, and could be continued for a maximum duration of 12 weeks. Patients who discontinued Initial Randomized Therapy (either voriconazole or amphotericin B) because of toxicity, intolerance or clinical failure were allowed to receive Other Licensed Antifungal Therapy.

One hundred and ninety six patients received voriconazole and 185 patients received amphotericin B as their initial randomized treatment and were included in the Safety Population. The most common underlying disease causing immunosuppression was malignant neoplasm of the lymphatic/hematopoietic tissues at baseline (voriconazole 114/196, 58.2%, amphotericin B 108/185, 58.4%).

Before switching to oral therapy, the duration of treatment with intravenous voriconazole was comparable to duration of treatment with intravenous amphotericin B. Overall, patients in the voriconazole group remained on initial randomized therapy longer than those in the amphotericin B group (Table 8-8).

Table 8-8 Global Aspergillosis Study (307/602) - Duration of Initial Randomized Therapy (Elapsed) – Safety Population

Route of administration	Duration of therapy (days)* Median (range)	
	Voriconazole Initial Randomized Therapy (N = 196)	Amphotericin B Initial Randomized Therapy (N = 185)
Oral therapy	76 (2 – 232)	N/A
Intravenous	10 (2 – 85)	12 (1 – 84)
Total	73 (2 – 288)	12 (1 – 84)

N/A = not applicable
*Elapsed time

8.6.1.1 Discontinuations from Initial Randomized Therapy Due to Adverse Events

One hundred patients (51%) in the voriconazole arm and 171 patients (92%) in the amphotericin B arm discontinued from Initial Randomized Therapy. The safety-related reasons for discontinuation from Initial Randomized Therapy are summarized in Table 8-9.

Table 8-9 Global Comparative Aspergillosis Study (307/602) - Reasons for Permanent Discontinuations from Initial Randomized Therapy – Safety Population

Reason for discontinuation including death**		Voriconazole Initial Randomized Therapy# (N = 196) n (%)	Amphotericin B Initial Randomized Therapy# (N = 185) n (%)
Death		21 (11)	19 (10)
Related to study drug	Insufficient clinical response	23 (12)	25 (14)
	Adverse event	15 (8)	35 (19)
	Laboratory abnormality	5 (3)	55 (30)
Not related to study drug	Adverse event	18 (9)	11 (6)
	Laboratory abnormality	2 (1)	2 (1)
	Other[a]	16 (8)	24 (13)

[a] Includes protocol violation, lost to follow up, did not meet study entry criteria, withdrawn consent and 'other'
**Patients can discontinue for more than one reason
#Duration of Initial Randomized Therapy in the voriconazole arm was 73 days (median, elapsed time) and 12 days (median, elapsed time) in the amphotericin B arm.

A greater proportion of patients receiving amphotericin B discontinued because of adverse events or laboratory abnormalities (40 patients in the voriconazole arm [20.4%] vs. 103 patients in the amphotericin B arm [55.7%]). Most patients (55.7%) in the amphotericin B group discontinued Initial Randomized Therapy because of adverse events (24.9%) or laboratory abnormalities (30.8%). Table 8-10 lists the discontinuations due to selected adverse events and due to laboratory abnormalities.

Table 8-10 Global Comparative Aspergillosis Study (307/602) – Reasons for Discontinuation from Initial Randomized Therapy Due to Selected Adverse Events and Laboratory Abnormalities – Safety Population

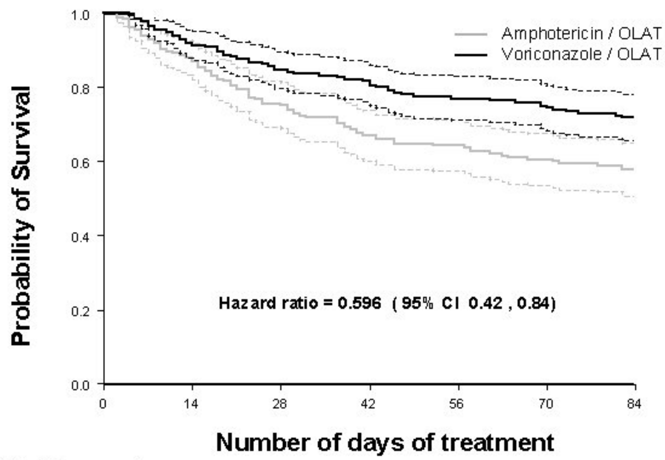
	Voriconazole Initial Randomized Therapy (N = 196) n (%)	Amphotericin B Initial Randomized Therapy (N = 185) n (%)
Patients with adverse events	194 (99.0)	177 (95.7)
Discontinuations due to adverse events	40 (20.4)	92 (49.7)
Mucor infection	3 (2)	0
Fungal infection	3 (2)	2 (1)
Acute kidney failure	2 (1)	13 (7)
Nausea	2 (1)	1 (<1)
Hallucinations	2 (1)	0
Abnormal vision	2 (1)	0
Rash	2 (1)	1 (<1)
Sepsis	2 (1)	0
Discontinuations due to laboratory abnormalities		
Abnormal LFT	2 (1)	1 (<1)
Increased hepatic enzymes	1 (<1)	0
Increased alkaline phosphatase	1 (<1)	0
Increased ALT	1 (<1)	1 (<1)
Increased AST	1 (<1)	0
Increased bilirubin	1 (<1)	2 (1)
Increased creatinine	0	38 (20.5)

ALT = alanine transaminase; AST = aspartate transaminase; LFT = liver function tests

8.6.1.2 Deaths and Serious Adverse Events

A survival benefit was seen for the voriconazole regimen compared to the amphotericin B regimen, through Day 84, in the Safety population, Figure 8-1.

Figure 8-1 Global Comparative Aspergillosis Study (307/602) – Kaplan-Meier Survival Plot – Safety Population



At Risk (Censored)

Vori	196 (0)	179 (0)	166 (0)	158 (0)	151 (0)	146 (0)	140 (0)
AMB	185 (0)	161 (0)	139 (0)	124 (0)	119 (0)	112 (0)	107 (0)

The proportion of patients surviving was consistently higher on the voriconazole arm than on the amphotericin B arm throughout the study. By Day 84, survival in the voriconazole arm was higher than in the comparator arm (0.714 *vs.* 0.578).

The total number of deaths occurring within 30 days of the End of Therapy in patients treated with the voriconazole regimen was 59 (30.1%) and the total in patients treated with the amphotericin B regimen was 61 (33.0%). Most deaths were judged to have been caused by factors other than the study drug. Only eight deaths were attributed to study drug. For one death in the voriconazole-treated patients, the investigator could not rule out voriconazole as a cause of the events leading to the outcome of death. In this patient, the causes of death were multi-organ failure and mycobacterial pneumonia. For seven deaths in the amphotericin B-treated patients, a relationship to study drug could not be ruled out. Patients in the amphotericin B group whose death was attributed to the study drug by the investigator had the following causes of death: respiratory failure, respiratory insufficiency and elevated creatinine levels, respiratory insufficiency, Cytomegalovirus pneumonia, respiratory failure and diffuse alveolar hemorrhage, progression of *Aspergillus* pneumonia and acute respiratory distress syndrome and Cytomegalovirus pneumonia and *Pneumocystis carinii*.

The serious adverse events most frequently reported in the voriconazole treatment arm are summarized in Table 8-11.

Table 8-11 Global Comparative Aspergillosis Study (307/602) – Most Frequently Reported Serious Adverse Events Occurring During Therapy or Within 30 Days of End of Therapy – Safety Population

Serious adverse events*	Voriconazole/OLAT** (N=196) n (%)	Amphotericin B/OLAT# (N=185) n (%)
Patients with serious adverse events	131 (66.8)	129 (69.7)
Serious adverse events*		
Pneumonia	24 (12.2)	15 (8.1)
Sepsis	19 (9.7)	15 (8.1)
Respiratory insufficiency	17 (8.7)	25 (13.5)
Fever	16 (8.2)	9 (4.9)
Dyspnea	13 (6.6)	14 (7.6)
Circulatory failure	11 (5.6)	7 (3.9)
Cardiac failure	9 (4.6)	6 (3.2)
Acute granulocytic leukemia	8 (4.1)	7 (3.9)
Graft *vs.* host disease	8 (4.1)	4 (2.2)
Infection fungal	7 (3.6)	15 (8.1)

*Most frequently reported in voriconazole group,
**Voriconazole/OLAT = Therapy with voriconazole Initial Randomized Therapy or switch from voriconazole to Other Licensed Antifungal Therapy
#Amphotericin B/OLAT = Therapy with amphotericin B Initial Randomized Therapy or switch from amphotericin B to Other Licensed Antifungal Therapy

The serious adverse events reported within the study mostly reflect underlying disease or disease under study. Table 8-12 presents the serious adverse events occurring more frequently in one of the treatment groups.

Table 8-12 Global Comparative Aspergillosis Study (307/602) –Serious Adverse Events Occurring During Therapy or Within 30 Days of End of Therapy Occurring More Frequently in Voriconazole or Amphotericin B Patients (Difference of ≥5 Events) – Safety Population

Serious adverse events*	Voriconazole/OLAT** (N = 196) n (%)	Amphotericin B/OLAT# (N = 185) n (%)
Fever	16 (8.2)	9 (4.9)
Lymphoma malignant	3 (1.5)	9 (4.9)
Infection fungal	7 (3.6)	15 (8.1)
Pneumonia	24 (12.2)	15 (8.1)
Respiratory insufficiency	17 (8.7)	25 (13.5)
Respiratory tract infection	5 (2.6)	12 (6.5)
Creatinine increased	1 (0.5)	9 (4.9)
Renal failure acute	1 (0.5)	8 (4.3)

*Serious adverse events with difference in number of events between treatment groups of >5 events
**Voriconazole/OLAT = Therapy with voriconazole Initial Randomized Therapy or switch from voriconazole to Other Licensed Antifungal Therapy, median duration of therapy (elapsed time) = 87 days (range 3 – 288)
#Amphotericin B/OLAT = Therapy with amphotericin B Initial Randomized Therapy or switch from amphotericin B to Other Licensed Antifungal Therapy, median duration of therapy (elapsed time) = 57 days (range 1 – 135)

8.6.1.3 Treatment Emergent Adverse Events

Patients randomized to voriconazole Initial Randomized Therapy had a longer total study drug exposure than patients receiving amphotericin B (median 73 days, 12,813 patient-days *vs.* median, 12 days, 2,896 patient-days, respectively). The difference was because many more patients discontinued Initial Randomized Therapy in the amphotericin B group than in the voriconazole group. As a result of this imbalance, the occurrence of any adverse event was likely to be higher for patients receiving voriconazole compared to amphotericin B, simply because of the longer period of observation. In this study, the number of patient-days of drug exposure for the regimen of amphotericin B followed by Other Licensed Antifungal Therapy (11,243 days) was comparable to the number of patient-days of drug exposure for treatment with voriconazole alone (12,813 days). Therefore, except as otherwise noted, the safety comparison discussed below is between voriconazole and amphotericin B + Other Licensed Antifungal Therapy (also referred to as amphotericin B/OLAT). Table 8-13 lists the adverse events most frequently reported in the voriconazole treatment arm.

Table 8-13 Global Comparative Aspergillosis Study (307/602) – Most Frequently Reported Adverse Events – Safety Population

Adverse event*	Voriconazole Initial Randomized Therapy (N = 196) n (%)	Amphotericin B/OLAT** (N = 185) n(%)
Abnormal vision	65 (33.2)	8 (4.3)
Fever	56 (28.6)	68 (36.8)
Nausea	46 (23.5)	61 (33.0)
Rash	45 (23.0)	40 (21.6)
Vomiting	43 (21.9)	53 (28.6)
Headache	37 (18.9)	27 (14.6)
Sepsis	35 (17.9)	25 (13.5)
Peripheral Edema	34 (17.3)	36 (19.5)
Diarrhea	34 (17.3)	50 (27.0)
Dyspnea	31 (15.8)	30 (16.2)

OLAT = Other Licensed Antifungal Therapy
*Most frequently reported in voriconazole group
**Amphotericin B/OLAT = Therapy with amphotericin B Initial Randomized Therapy or switch from amphotericin B to Other Licensed Antifungal Therapy

Table 8-14 lists the adverse events that were reported with different frequencies between treatment cohorts (>5% difference).

Table 8-14 Global Comparative Aspergillosis Study (307/602) –Adverse Events Reported More Frequently in Voriconazole or Amphotericin B Patients – Safety Population

Adverse events*	Voriconazole Initial Randomized Therapy (N = 196) n (%)	Amphotericin B/OLAT** (N = 185) n (%)
Abnormal vision	65 (33.2)	8 (4.3)
Fever	56 (28.6)	68 (36.8)
Nausea	46 (23.5)	61 (33.0)
Vomiting	43 (21.9)	53 (28.6)
Diarrhea	34 (17.3)	50 (27.0)
Abdominal pain	27 (13.8)	40 (21.6)
Respiratory disorder	22 (11.2)	31 (16.8)
Hypokalemia	18 (9.2)	47 (25.4)
Creatinine increased	10 (5.1)	64 (34.6)
Chills	9 (4.6)	43 (23.2)
Hypotension	9 (4.6)	19 (10.3)
Acute kidney failure	7 (3.6)	89 (48.1)
Hypomagnesemia	7 (3.6)	21 (11.4)
Hyperglycemia	5 (2.6)	19 (10.3)

OLAT = Other Licensed Antifungal Therapy
*Adverse events with difference in frequency between treatment groups of >5%
**Amphotericin B/OLAT = Therapy with amphotericin B Initial Randomized Therapy or switch from amphotericin B to Other Licensed Antifungal Therapy

Thirteen of the 14 events occurred more frequently in patients during the amphotericin B regimen than in patients receiving voriconazole Initial Randomized Therapy. These events were mostly related to renal dysfunction or infusion related toxicity, and were consistent with the known safety profile of conventional amphotericin B. Only abnormal vision occurred at a higher frequency (>5% difference) in patients treated with voriconazole Initial Randomized Therapy than patients who received the amphotericin B regimen. Although the difference in frequencies was not greater than 5%, hallucinations also occurred at a higher rate in patients treated with voriconazole (13 [6.6%] in the voriconazole Initial Randomized Therapy arm versus three [1.6%] in the amphotericin B regimen arm).

8.6.1.4 Visual Function Tests

Bedside visual acuity assessment, visual field testing and funduscopy were performed at study entry, End of Therapy and at the follow up visit. Most patients did not have clinically meaningful changes in the results of these tests.

8.6.1.5 Laboratory Abnormalities

Laboratory test abnormalities irrespective of baseline abnormalities are presented in Table 8-15.

Table 8-15 Global Comparative Aspergillosis Study (307/602) - Clinically Significant Laboratory Test Abnormalities Irrespective of Baseline Abnormalities – Safety Population

Laboratory Parameter	Units	Criterion	Voriconazole Initial Randomized Therapy (N = 196) n/N (%)	Amphotericin B/OLAT* (N = 185) n/N (%)
Hematology				
RBC Count	10^6 /mm^3	<0.8 x BL	33/180 (18.3)	52/177 (29.4)
ANC	10^3 /mm^3	<0.8 x LLN	90/162 (55.6)	79/158 (50.0)
WBC count	10^3 /mm^3	<2.5 x 10^3/mm^3	106/180 (58.9)	96/178 (53.9)
Platelets	10^3 /mm^3	<75 x 10^3/mm^3	131/178 (73.6)	133/177 (75.1)
Liver function				
Total bilirubin	mg/dL	>1.5 x ULN	35/180 (19.4)	46/173 (26.6)
AST	IU/L	>3 x ULN	21/180 (11.7)	18/174 (10.3)
ALT	IU/L	>3 x ULN	34/180 (18.9)	40/173 (23.1)
Alkaline phosphatase	IU/L	>3 x ULN	29/181 (16.0)	38/173 (22.0)
Renal function				
Serum creatinine	mg/dL	>1.3 x ULN	39/182 (21.4)	102/177 (57.6)
BUN	mg/dL	>1.3 x ULN	25/63 (39.7)	49/62 (79.0)
Serum potassium	mEq/L	<0.9 x ULN	30/181 (16.6)	70/178 (39.3)

ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; BL = baseline; BUN = blood urea nitrogen; LLN = lower limit of normal; OLAT = Other Licensed Antifungal Therapy; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell
*Amphotericin B/OLAT = Therapy with amphotericin B Initial Randomized Therapy or switch from amphotericin B to Other Licensed Antifungal Therapy

Almost all patients had at least one clinically significant laboratory abnormality during the course of the study (181/184 patients in the voriconazole Initial Randomized Therapy arm, 98.4% and 180/180 patients in the amphotericin B + Other Licensed Antifungal Therapy group, 100%).

The pattern of laboratory abnormalities was generally similar between the voriconazole Initial Randomized Therapy and amphotericin B + Other Licensed Antifungal Therapy groups, except for changes relating to renal dysfunction (*e.g.* increased serum creatinine, increased BUN, and hypokalemia) which were more frequent in patients in the amphotericin B + Other Licensed Antifungal Therapy group. This was consistent with the known toxicity profile of conventional amphotericin B. The proportions of patients with hepatic laboratory abnormalities were similar between the voriconazole Initial Randomized Therapy and amphotericin B + Other Licensed Antifungal Therapy cohorts.

8.6.1.6 Conclusions

There was a survival benefit for the voriconazole regimen compared to amphotericin B regimen. The proportion of patients surviving was consistently higher on the voriconazole arm than on the amphotericin B arm throughout the study.

Comparison of the safety data from the two populations with similar duration of exposure, the voriconazole Initial Randomized Therapy and the amphotericin B + Other Licensed Antifungal Treatment regimen shows that the safety and toleration of voriconazole was superior to amphotericin B + Other Licensed Antifungal Therapy. With the exception of visual disturbances, the majority of adverse events were reported at a lower rate in the voriconazole group. Hepatic function laboratory abnormalities occurred at a similar frequency in both treatment arms, and renal function laboratory abnormalities occurred more often in the amphotericin B + Other Licensed Antifungal Therapy group.

8.6.2 Empirical Therapy Study (603/MSG42)

In the Empirical Therapy Study (603/MSG42), patients with persistent fever and neutropenia were randomized to either voriconazole or liposomal amphotericin B. Voriconazole was administered as an intravenous loading dose of 6mg/kg q 12 h for two doses followed by 3mg/kg q 12 h. After at least three days of intravenous administration, voriconazole could be given as an oral maintenance dose of 200 mg q 12 h (or, for patients weighing less than 40kg, 100mg q 12 h). Liposomal amphotericin B was administered intravenously, at a dose of 3 mg/kg/day. Patients were treated for up to three days after recovery from neutropenia or for up to 12 weeks, in the event of a confirmed fungal infection. Four hundred twenty-one patients were randomized to voriconazole and 428 patients were randomized to liposomal amphotericin B and are included in the Safety population. The most frequent underlying disease causing immunosuppression was newly diagnosed leukemia, which occurred in 132 of 421 voriconazole patients (31.4%) and 132 of 428 liposomal amphotericin B patients (30.8%). Two hundred and two voriconazole patients (48.0%) and 220 liposomal amphotericin B patients (51.4%) had bone marrow transplants.

The duration of treatment is summarized in Table 8-16.

Table 8-16 Empirical Therapy Study (603/MSG42) - Duration of Treatment* – Safety Population

	Voriconazole (N = 421)	Liposomal amphotericin B (N = 428)
Total duration of treatment (days)		
Mean	11	10
Median	7	7
(%) subjects receiving randomized treatment for:		
≤1 day	4 (1.0)	19 (4.4)
2 – 7 days	216 (51.3)	202 (47.2)
8 – 14 days	126 (29.9)	125 (29.2)
15 – 21 days	44 (10.5)	50 (11.7)
22 – 28 days	8 (1.9)	13 (3.0)
≥29 days	23 (5.5)	19 (4.4)

*Elapsed time

The median duration of intravenous treatment with study drug was similar for voriconazole and liposomal amphotericin B patients (six and seven days, respectively). Oral treatment was received by 92 voriconazole patients, with a median duration of six days.

8.6.2.1 Discontinuations due to Adverse Events

There were 111 voriconazole patients (26.4%) and 93 liposomal amphotericin B-treated patients (21.7%) who discontinued from the study. All reasons for discontinuation can be found in Section 7.2.1. The safety-related reasons recorded by the investigator for discontinuation are summarized in Table 8-17.

Table 8-17 Empirical Therapy Study (603/MSG42) - Reasons for Permanent Discontinuation – Safety Population

Reason for discontinuation including death		Voriconazole (N = 421) n (%)	Liposomal amphotericin B (N = 428) n (%)
Death		19 (4.5)	21 (4.9)
Related to study drug	Insufficient clinical response	27 (6.4)	6 (1.4)
	Adverse event	17 (4.0)	25 (5.8)
	Laboratory abnormality	6 (1.4)	2 (0.5)
Not related to study drug	Adverse event	16 (3.8)	5 (1.2)
	Laboratory abnormality	4 (1.0)	6 (1.4)
	Other[a]	22 (5.2)	28 (6.5)

[a] Includes protocol violation, lost to follow up, did not meet entry criteria, withdrawn consent and 'other'

More patients on voriconazole discontinued due to insufficient clinical response. A similar number of patients in both arms discontinued due to adverse events and laboratory test abnormalities. The adverse events or laboratory abnormalities most frequently leading to discontinuation from voriconazole are shown in Table 8-18.

Table 8-18 Empirical Therapy Study (603/MSG42) - Adverse Events and Laboratory Abnormalities Leading to Discontinuation – Safety Population

Adverse event	Voriconazole (N=421) n (%)	Liposomal amphotericin B (N = 428) n (%)
Patients with adverse events	417 (99.0)	423 (98.8)
Discontinuations due to adverse events and laboratory abnormalities	43 (10.2)	38 (8.9)
Acute kidney failure	12 (2.9)	1 (0.2)
Hallucinations	4 (1.0)	0
Sepsis	3 (0.7)	1 (0.2)
Hypotension	3 (0.7)	1 (0.2)
Dementia	3 (0.7)	0
Bilirubinemia	3 (0.7)	1 (0.2)
Liver function tests abnormal	3 (0.7)	4 (0.9)
Fever	2(0.5)	0
Rash	2 (0.5)	3 (0.7)
Abnormal vision	2 (0.5)	0

Although more patients discontinued due to acute kidney failure in the voriconazole group (12/421, 2.9%) than in the liposomal amphotericin B group (1/428, 0.2%), fewer voriconazole patients (43/410, 10.5%) had increases in serum creatinine of ≥1.5x baseline than liposomal amphotericin B patients (80/412, 19.4%).

Adverse events leading to temporary discontinuations or dose reductions occurred in 14 of 421 voriconazole patients (3.3%) and 59 of 428 liposomal amphotericin B patients (13.8%).

8.6.2.2 Deaths and Serious Adverse Events

Sixty two voriconazole patients and 46 liposomal amphotericin B patients died on therapy or within 30 days of the end of therapy. Most of these patients died due to other illnesses (including but not limited to sepsis, pneumonia, leukemia) or other causes (including but not limited to graft *vs.* host disease and chemotherapy). The investigator assigned the causality of the event leading to death for two patients in the voriconazole group as study drug, meaning that a relationship to voriconazole could not be ruled out. The causes of death for these two cases were: ventricular fibrillation, medullary hypoplasia, and myeloid leukemia for one patient and acute leukemia, pneumonia, and renal failure for the second patient.

The serious adverse events most frequently reported in the voriconazole patients, are summarized in Table 8-19.

Table 8-19 Empirical Therapy Study (603/MSG42) – Most Frequently Reported Serious Adverse Events Occurring During Therapy or Within 30 Days of End of Therapy – Safety Population

Serious adverse events*	**Voriconazole (N = 421) n (%)**	**Liposomal amphotericin B (N = 428) n (%)**
Patients with serious adverse events	101 (24.0)	109 (25.5)
Serious adverse events		
Sepsis	41 (9.7)	29 (6.8)
Renal failure acute	27 (6.4)	17 (4.0)
Dyspnea	25 (5.9)	24 (5.6)
Respiratory insufficiency	21 (5.0)	27 (6.3)
Leukemia granulocytic acute	20 (4.8)	7 (1.6)
Pneumonia	15 (3.6)	19 (4.4)
Circulatory failure	13 (3.1)	6 (1.4)
Fever	13 (3.1)	17 (4.0)
Graft *vs.* host disease	12 (2.9)	6 (1.4)
Cardiac arrest	11 (2.6)	6 (1.4)
Hypotension	11 (2.6)	7 (1.6)

*Most frequently reported in voriconazole group

Sepsis was the most frequently reported serious adverse event on voriconazole and was reported more frequently than in liposomal amphotericin B patients. See Section 8.8.5 for a complete discussion on sepsis as an adverse event in the voriconazole program.

8.6.2.3 Treatment Emergent Adverse Events

The treatment-emergent adverse events (all causality) most frequently reported by voriconazole patients are summarized in Table 8-20.

Table 8-20 Empirical Therapy Study (603/MSG42) – Most Frequently Reported Adverse Events – Safety Population

Adverse event*	Voriconazole (N = 421) n (%)	Liposomal amphotericin B (N = 428) n (%)
Fever	132 (31.4)	168 (39.3)
Abnormal vision	110 (26.1)	21 (4.9)
Chills	97 (23.0)	177 (41.4)
Rash	96 (22.8)	105 (24.5)
Vomiting	90 (21.4)	93 (21.7)
Nausea	85 (20.2)	99 (23.1)
Peripheral edema	69 (16.4)	87 (20.3)
Headache	66 (15.7)	47 (11.0)
Hypotension	66 (15.7)	65 (15.2)
Abdominal pain	65 (15.4)	91 (21.3)

*Most frequently reported in voriconazole patients

In addition to the safety analyses presented above, infusion related reactions, hepatic and renal adverse events and visual function reported during the Empirical Therapy Study (603) were examined in greater detail.

Infusion Related Reactions

Adverse events occurring during study drug infusions were prospectively defined and monitored by the investigator. The most frequently reported infusion related reactions are summarized in Table 8-21.

Table 8-21 Empirical Therapy Study (603/MSG42) – Most Frequently Reported Treatment-Related Infusion Related Reactions – Safety Population

Adverse event*	Voriconazole (N = 421) n (%)	Liposomal amphotericin B (N = 428) n (%)
Abnormal vision	91 (21.6)	3 (0.7)
Fever	77 (18.3)	120 (28.0)
Chills	52 (12.4)	118 (27.6)
Nausea	32 (7.6)	48 (11.2)
Vomiting	29 (6.9)	46 (10.7)
Tachycardia	24 (5.7)	37 (8.6)
Hypertension	21 (5.0)	34 (7.9)
Vasodilation	13 (3.1)	45 (10.5)
Dyspnea	1 (0.2)	33 (7.7)
Hypotension	23 (5.5)	24 (5.6)
Headache	12 (2.9)	14 (3.3)
Chest pain	1 (0.2)	17 (4.0)

*Includes the ten most frequently reported adverse events in liposomal amphotericin B and voriconazole patients.

Table 8-22 Empirical Therapy Study (603/MSG42) – Most Frequently Reported Treatment-Related Infusion Related Reactions Occurring More Frequently in Voriconazole Patients than in Liposomal Amphotericin B Patients – Safety Population

Adverse event*	Voriconazole (N = 421) n (%)	Liposomal amphotericin B (N = 428) n (%)
Abnormal vision	91 (21.6)	3 (0.7)
Hallucinations	11 (2.6)	1 (0.2)

*Events occurred at least twice as frequently in voriconazole patients or in at least 10 voriconazole patients for events which occurred in five or fewer lipsosomal amphotericin B patients

Table 8-23 Empirical Therapy Study (603/MSG42) – Most Frequently Reported Treatment-Related Infusion Related Reactions Occurring More Frequently in Liposomal Amphotericin B Patients than in Voriconazole Patients – Safety Population

Adverse event*	Voriconazole (N = 421) n (%)	Liposomal amphotericin B (N = 428) n (%)
Chills	52 (12.4)	118 (27.6)
Vasodilation	13 (3.1)	45 (10.5)
Tachycardia	24 (5.7)	37 (8.6)
Dyspnea	1 (0.2)	33 (7.7)
Chest pain	1 (0.2)	17 (4.0)
Cough increased	2 (0.5)	15 (3.5)
Back pain	0	13 (3.0)

*Events occurred at least twice as frequently in liposomal amphotericin B patients or in at least 10 liposomal amphotericin B patients for events which occurred in five or fewer voriconazole patients.

Hepatic Abnormalities

Review of alanine transaminase, aspartate transaminase, total bilirubin, and alkaline phosphatase laboratory data showed little difference between treatment groups. These data are summarized in Table 8-24.

Table 8-24 Empirical Therapy Study (603/MSG42) – Clinically Significant Hepatic Chemistry Laboratory Abnormalities – Safety Population

Laboratory abnormality	Voriconazole (N =421) n/N (%)	Liposomal amphotericin B (N = 428) n/N (%)
AST increase of ≥ 5 x BL if BL < 2 x ULN	37/396 (9.3)	27/394 (6.9)
ALT increase of ≥ 5 x BL if BL < 2 x ULN	29/386 (7.5)	34/376 (9.0)
Alkaline phosphatase increase of ≥ 5 x BL if BL < 2 x ULN	12/400 (3.0)	19/396 (4.8)
Total bilirubin increase of ≥ 1.5 x BL	73/401 (18.2)	98/394 (24.9)
Total bilirubin increase of ≥ 3 x BL	40/401 (10.0)	46/394 (11.7)

ALT = alanine transaminase; AST = aspartate transaminase; BL = Baseline; ULN = Upper Limit of Normal

Renal Adverse Events and Serum Creatinine Abnormalities

A summary of renal adverse events is shown in Table 8-25.

Table 8-25 Empirical Therapy Study (603/MSG42) - Renal Adverse Events and Clinically Significant Serum Creatinine Laboratory Abnormalities – Safety Population

	Voriconazole (N = 421) n (%)		**Liposomal amphotericin B (N = 428) n (%)**	
Adverse event	**All severity**	**Severe**	**All severity**	**Severe**
Acute kidney failure	25 (5.9)	16 (3.8)	18 (4.2)	10 (2.3)
Abnormal kidney function	21 (5.0)	3 (0.7)	34 (7.9)	6 (1.4)
Increased creatinine	16 (3.8)	3 (0.7)	36 (8.4)	1 (0.2)
Hypokalemia	60 (14.3)	2 (0.5)	106 (24.8)	3 (0.7)
Laboratory abnormality				
Number of patients with serum creatinine laboratory values	410		412	
Increase ≥ 1.5 x BL n (%)	43 (10.5)		80 (19.4)	
Increase ≥2 x BL n (%)	29 (7.1)		32 (7.8)	
Increase ≥3 x BL n (%)	19 (4.6)		21 (5.1)	

BL = baseline

Whereas acute kidney failure was more frequent in voriconazole-treated patients, abnormal kidney function, increased creatinine and hypokalemia were reported more often with liposomal amphotericin B than with voriconazole. Review of creatinine shifts from baseline also showed that fewer voriconazole patients had an elevation in creatinine relative to baseline, when compared with liposomal amphotericin B patients.

8.6.2.4 Visual Function Tests

Bedside visual acuity assessment, visual field testing and funduscopy were performed at study entry, End of Therapy and at the follow up visit. Most patients did not have clinically meaningful changes in the results of these tests and there was no difference between the voriconazole and liposomal amphotericin B groups.

8.6.2.5 Laboratory Abnormalities

Laboratory abnormalities irrespective of baseline abnormalities are summarized in Table 8-26.

Table 8-26 Empirical Therapy Study (603/MSG42) – Clinically Significant Laboratory Abnormalities Irrespective of Baseline Abnormality – Safety Population

Laboratory parameter	Units	Criterion	Voriconazole (N = 421) n/N (%)	Liposomal amphotericin B (N = 428) n/N (%)
Hematology				
RBC Count	10^6 /mm^3	<0.8 x BL	14/414 (3.4)	24/414 (5.8)
ANC	10^3 /mm^3	<0.5 x LLN	82/89 (92.1)	89/100 (89.0)
WBC count	10^3 /mm^3	<2.5 x 10^3/mm^3	396/414 (95.7)	394/415 (94.9)
Platelets	10^3 /mm^3	<75 x 10^3/mm^3	402/414 (97.1)	397/413 (96.1)
Liver function				
Total bilirubin	mg/dL	>1.5 x ULN	106/400 (26.5)	128/393 (32.6)
AST	IU/L	>3 x ULN	22/396 (5.6)	17/393 (4.3)
ALT	IU/L	>3 x ULN	30/385 (7.8)	25/374 (6.7)
Alkaline Phosphatase	IU/L	>3 x ULN	27/399 (6.8)	26/394 (6.6)
Renal function				
Serum Creatinine	mg/dL	>1.3 x ULN	54/410 (13.2)	66/411 (16.1)
Blood urea nitrogen	mg/dL	>1.3 x ULN	96/401 (23.9)	113/402 (28.1)
Serum potassium	mEq/L	<0.9 x LLN	101/413 (24.5)	165/413 (40.0)

ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; BL = baseline; BUN = blood urea nitrogen; LLN = lower limit of normal; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell

The frequency of laboratory abnormalities was similar between the groups. The high frequency of hematological abnormalities is consistent with the underlying conditions of the majority of these patients.

8.6.2.6 Conclusions

Sixty-two voriconazole patients and 46 liposomal amphotericin patients died during the study or within 30 days of the end of therapy. In two voriconazole-treated patients who died, the investigator could not rule out voriconazole as a cause of death. The causes of death for these two patients were ventricular fibrillation, medullary hypoplasia, and myeloid leukemia for one patient and acute leukemia, pneumonia, and renal failure for the other patient.

Patients receiving voriconazole had more frequent visual disturbances. Whereas acute kidney failure was more frequent in voriconazole-treated patients, abnormal kidney function, increased creatinine and hypokalemia were reported more often with liposomal amphotericin B. More patients discontinued due to acute kidney failure in the voriconazole group (12/421; 2.9%) than in the liposomal amphotericin B group (1/428; 0.2%). However, when the number of patients with significant increases in serum creatinine are examined, fewer patients had significant increases in serum creatinine (≥1.5 x baseline) in the voriconazole group (43/410, 10.5%) than in the liposomal amphotericin B group (80/412, 19.4%).

Liver function test changes were similar in the two treatment groups and there was no difference in visual function testing between the two groups. Finally, there was a higher frequency of infusion related reactions with liposomal amphotericin B. Overall the results of the Empirical Therapy Study (603) support the safety of voriconazole as empirical therapy in patients with fever and neutropenia.

8.6.3 Esophageal Candidiasis Study (305)

In the double-blind, double-dummy Esophageal Candidiasis Study (305), immunocompromised patients with esophageal candidiasis were randomized to either voriconazole administered orally at a dose of 200mg bid or fluconazole 400mg once daily on Day one followed by maintenance dosing of 200mg once daily. Study treatment could be administered from two to six weeks. Three hundred ninety-one patients were randomized and received at least one dose of study treatment (n=200 voriconazole-treated patients and n=191 fluconazole-treated patients). All randomized patients were included in the analysis of safety, the Intention to Treat population. The majority of patients in both groups had HIV infection and 114/191 (59.7%) fluconazole patients had baseline CD4 counts of less than 50 cells/mm^3, suggesting advanced AIDS was present in the majority of patients.

Patients in the voriconazole group received from one to 45 days of therapy with a median duration of 14 days, and patients in the fluconazole group received two to 49 days of therapy with a median of 15 days of treatment.

8.6.3.1 Discontinuations Due to Adverse Events

There were 69 (34.5%) voriconazole- and 55 (28.8%) fluconazole-treated patients who discontinued from the study. The safety-related reasons given by the investigator for discontinuation are summarized in Table 8-27.

Table 8-27 **Esophageal Candidiasis Study (305) -Reasons for Permanent Discontinuation – Intention to Treat Population**

Reasons for discontinuation including death		Voriconazole (N = 200) n (%)	Fluconazole (N = 191) n (%)
Death		12 (6.0)	12 (6.3)
Related to study drug	Insufficient clinical response	4 (2.0)	5 (2.6)
	Adverse event	5 (2.5)	1 (0.5)
	Lab abnormality	7 (3.5)	2 (1.0)
Not related to study drug	Adverse event	9 (4.5)	4 (2.1)
	Lab abnormality	1 (0.5)	1 (0.5)
	Other[a]	31 (15.5)	30 (15.7)

[a] Includes protocol violation, lost to follow up, did not meet entry criteria, withdrawn consent, no pathogen isolated from pre-treatment specimen and 'other'

The ten most commonly reported adverse events or laboratory abnormalities leading to discontinuation from the study are presented in Table 8-28.

Table 8-28 Esophageal Candidiasis Study (305) - Most Frequent Adverse Events and Laboratory Abnormalities Leading to Discontinuation – Intention to Treat Population

	Voriconazole (N = 200) n%	Fluconazole (N = 191) n%
Patients with adverse events	159 (79.5)	141 (73.8)
Discontinuations due to adverse events	22 (11.0)	8 (4.2)
Alkaline phosphatase increased	4 (2.0)	3 (1.6)
Abnormal vision	3 (1.5)	0
Rash	2 (1.0)	0
Pneumonia	2 (1.0)	1 (0.5)
Vomiting	2 (1.0)	0
Somnolence	2 (1.0)	0
Abdominal pain	2 (1.0)	0
Confusion/headache	2 (1.0)	0
Cholestatic jaundice	2 (1.0)	0
Atrial fibrillation	1 (0.5)	0

Other reasons for discontinuation, occurring in one patient each in the voriconazole arm: chills, convulsion, abnormal accommodation, nausea, hypertension, tachycardia, fever, abscess, hepatitis, increased creatinine, abnormal kidney function, increased hepatic enzymes, jaundice

The proportion of patients who discontinued due to adverse events was higher in the voriconazole group (23 [11.5%]) than in the fluconazole group (8 [4.2%]).

8.6.3.2 Deaths and Serious Adverse Events

Fifteen (7.5%) voriconazole patients and 18 (9.4%) fluconazole patients died during the study, or within 30 days of the end of therapy (12 patients in each group died during the study). The investigator's assessment of causality for the majority of deaths, for both treatments, was either 'other illness' or 'other'. Common causes of death due to 'other illnesses' included HIV, pneumonia (including *Pneumocystis carinii* pneumonia), respiratory failure/depression and cardiorespiratory arrest. "Other" causes of death were lymphoproliferative disorder (in one voriconazole patient) and cardiorespiratory arrest (due to reduced food intake, in one fluconazole patient). All but one of the deaths were attributed by the investigator to underlying illness and were not attributed to study drug. One voriconazole patient died due to cardiorespiratory arrest and hypotension; the investigator could not rule out a possible interaction between lorazepam and voriconazole as the cause of the adverse events. The Sponsor did not consider this death related to voriconazole.

The serious adverse events most frequently reported in the voriconazole patients are listed in Table 8-29.

Table 8-29 Esophageal Candidiasis Study (305) - Most Frequently Reported Serious Adverse Events Occurring During Therapy or Within 30 Days of End of Therapy – Intention to Treat Population

Serious adverse events*	Voriconazole (N = 200) n (%)	Fluconazole (N = 191) n (%)
Pneumonia	9 (4.5)	8 (4.0)
HIV infection	7 (3.5)	11 (5.8)
Esophagitis	5 (2.5)	2 (1.0)
Pneumocystis carinii infection	4 (2.0)	3 (1.6)
Retinitis	3 (1.5)	1 (0.5)
Infection	3 (1.5)	4 (2.1)
Encephalopathy	3 (1.5)	1 (0.5)
Abdominal pain	3 (1.5)	1 (0.5)
Diarrhea	3 (1.5)	2 (1.0)
Vomiting	3 (1.5)	0

*Most frequently reported in voriconazole patients
Other serious adverse events in three subjects in voriconazole arm: dehydration, AIDS

The pattern and occurrence of serious adverse events was similar between the two treatment arms.

8.6.3.3 Treatment Emergent Adverse Events

The all causality treatment-emergent adverse events most frequently reported by voriconazole patients are summarized in Table 8-30.

Table 8-30 Esophageal Candidiasis Study (305) – Most Frequently Reported Adverse Events – Intention to Treat Population

Adverse event*	Voriconazole N = 200 n (%)	Fluconazole N = 191 n (%)
Abnormal vision	45 (22.5)	15 (7.9)
Fever	24 (12.0)	16 (8.4)
Diarrhea	18 (9.0)	13 (6.8)
Vomiting	14 (7.0)	12 (6.3)
Alkaline phosphatase increased	13 (6.5)	7 (3.7)
Nausea	12 (6.0)	12 (6.3)
Rash	11 (5.5)	10 (5.2)
Headache	10 (5.0)	13 (6.8)
Herpes simplex infection	10 (5.0)	6 (3.1)
Infection bacterial	9 (4.5)	14 (7.3)
Constipation	9 (4.5)	6 (3.1)

*Most frequently reported in voriconazole patients

Abnormal vision was reported more than twice as frequently in voriconazole patients than in fluconazole patients. Among other adverse events, fever, diarrhea and increased alkaline phosphatase were reported more frequently in voriconazole patients and bacterial infection and gastritis were reported more frequently in fluconazole patients.

8.6.3.4 Visual Function Tests

Contrast sensitivity, visual acuity, color vision tests and funduscopy were performed at study entry, End of Therapy, and at the follow up visit four weeks after end of therapy. Most patients did not have clinically meaningful changes in the results of these tests and the results were similar between the treatment groups.

8.6.3.5 Laboratory Abnormalities

Laboratory abnormalities irrespective of baseline abnormalities are summarized in Table 8-31:

Table 8-31 Esophageal Candidiasis Study (305) – Clinically Signficant Laboratory Abnormalities Irrespective of Baseline Abnormality – Intention to Treat Population

Laboratory parameter	Units	Criterion	Voriconazole (N = 200) n/N (%)	Fluconazole (N = 191) n/N (%)
Hematology				
RBC count	$10^6/mm^3$	<0.8 x BL	7/186 (3.8)	9/186 (4.8)
ANC	$10^3/mm^3$	<0.5 x LLN	34/136 (25.0)	32/139 (23.0)
WBC count	$10^3/mm^3$	<2.5 x $10^3/mm^3$	60/186 (32.3)	71/186 (38.2)
Platelets	$10^3/mm^3$	<75 x $10^3/mm^3$	13/184 (7.1)	23/185 (12.4)
Liver function				
Total bilirubin	mg/dL	>1.5 x ULN	8/185 (4.3)	7/186 (3.8)
AST	IU/L	>3 x ULN	38/187 (20.3)	15/186 (8.1)
ALT	IU/L	>3 x ULN	20/187 (10.7)	12/186 (6.5)
Alkaline Phosphatase	IU/L	>3 x ULN	19/187 (10.2)	14/186 (7.5)
Renal function				
Creatinine	mg/dL	>1.3 x ULN	7/187 (3.7)	7/186 (3.8)
Urea	mg/dL	>1.3 x ULN	7/174 (4.0)	7/174 (4.0)

ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; BL = baseline; LLN = lower limit of normal; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell

More voriconazole than fluconazole patients had increases in ALT, AST and alkaline phosphatase.

8.6.3.6 Conclusions

The number of patients who died or had serious adverse events, was comparable in the two groups. The number of discontinuations in both groups was relatively low although a greater percentage of patients in the voriconazole group (11.5%) discontinued due to adverse events than in the fluconazole group (4.2%). Treatment emergent adverse events (all causality) were reported for 79.5% of patients in the voriconazole group and 73.8% in the fluconazole group. The rate of abnormal vision was higher in the voriconazole group (22.5% of patients) than in the fluconazole group (7.9% of patients). However, there was no difference in the results of the ophthalmologic safety tests between the two groups, either during or after completion of the study. More voriconazole than fluconazole patients had increased ALT, AST and alkaline phosphatase.

8.7 Pooled Safety Database

The composition of the pooled safety database subgroups is discussed in Section 8.1.

8.7.1 Therapeutic Studies and Overall Pooled Populations

8.7.1.1 Patient Exposure

1493 patients are included in the voriconazole Therapeutic Studies safety database. These 1493 patients received 62,692 days (172 years) of voriconazole treatment.

In the overall pooled safety database (N = 2090), patient voriconazole experience amounts to 127,382 days (349 years) and 558 patients have received >12 weeks of therapy. There are 38 patients in the compassionate use/extension program who received greater than one year of treatment. Exposure to voriconazole in the Therapeutic Studies and Overall Pooled populations is presented in Table 8-32.

Table 8-32 Pooled Safety Database – Duration of Treatment - Therapeutic Studies and Overall Pooled Populations

Duration of treatment (days)*	Voriconazole Therapeutic Studies (N = 1493)	Voriconazole Overall Pooled (N = 2090)
Median (range)	16 (1 – 326)	21 (1 – 800)
n (%) subjects receiving randomized treatment for:		
≤7	363 (24.3)	440 (21.1)
8-14	305 (20.4)	356 (17.0)
15-28	289 (19.4)	371 (17.8)
29-84	218 (14.6)	365 (17.5)
85-365	318 (21.3)	520 (24.9)
>365	0	38 (1.8)

*Actual time

8.7.1.2 Discontinuations due to Adverse Events

275 (18.4%) of 1493 patients in the Therapeutic Studies discontinued from the study due to adverse events or laboratory abnormalities (all causality). 339 (16.2%) of 2090 patients in the Overall Pooled population discontinued from study due to adverse events or laboratory abnormalities (all causality). The most frequent reasons for discontinuation in these two pooled populations are shown in Table 8-33.

Table 8-33 Pooled Safety Database – Most Frequent Adverse Events Leading to Discontinuation – Therapeutic Studies Population

Adverse events*	Voriconazole Therapeutic Studies (N = 1493) n (%)	Voriconazole Overall Pooled (N = 2090) n (%)
Patients with adverse events	1437 (96.2)	1960 (93.8)
Reasons for discontinuation**		
Elevated alkaline phosphatase	25 (1.7)	29 (1.4)
Acute kidney failure	23 (1.5)	28 (1.3)
Increased hepatic enzymes	19 (1.3)	20 (1.0)
Liver function tests abnormal	13 (0.9)	23 (1.1)
Rash	13 (0.9)	20 (1.0)
Bilirubinemia	12 (0.8)	14 (0.7)
Fungal infection	12 (0.8)	18 (0.9)
Sepsis	11 (0.7)	20 (1.0)
Cholestatic jaundice	10 (0.7)	10 (0.5)
Abnormal vision	8 (0.5)	11 (0.5)
Respiratory disorder	8 (0.5)	17 (0.8)
Fever	8 (0.5)	10 (0.5)
Hallucinations	8 (0.5)	8 (0.4)

*Most frequent = adverse events leading to discontinuation occurring in ≥8 patients in the Therapeutic Studies population
**Patients can discontinue for more than one reason.

In both the Therapeutic Studies and the Overall Pooled populations, the most common adverse events leading to discontinuation in the voriconazole patients were related to skin, hepatic and renal abnormalities. These abnormalities are specifically discussed in Section 8.7.

8.7.1.3 Deaths and Serious Adverse Events

469 (31.4%) of 1493 patients in the Therapeutic Studies died and 828 (39.6%) of 2090 in the Overall Pooled population died. Table 8-34 lists the most frequent causes of death in the Therapeutic Studies population with the corresponding occurrence in the Overall Pooled population.

Table 8-34 Pooled Safety Database – Most Frequently Reported Causes of Death – Deaths Occurring During Therapy or Within 30 Days of End of Therapy – Therapeutic Studies and Overall Pooled Populations

	Voriconazole Therapeutic Studies (N = 1493) n (%)#	**Voriconazole Overall Pooled (N = 2090) n (%)#**
Total number of deaths	469 (31.4)	828 (39.6)
Cause of death (preferred term)		
Septicemia	49 (3.3)	71 (3.4)
Aspergillosis	49 (3.3)	93 (4.4)
Acute myeloid leukemia	42 (2.8)	67 (3.2)
Ill-defined condition	42 (2.8)	70 (3.3)
Respiratory failure	33 (2.2)	80 (3.8)
Shock, without trauma	31 (2.1)	46 (2.2)
Cardiac arrest	24 (1.6)	32 (1.5)
Pneumonia	22 (1.5)	36 (1.7)
AIDS	19 (1.3)	29 (1.4)
Unspecified leukemia	16 (1.1)	23 (1.1)

#It should be noted that this table includes 2 deaths from two studies, Japanese Non-Comparative Deep-Seated Mycoses Study (1001) and the Comparative Paracoccidioides Study (1010). Patients from these studies are not included in the denominators for this table.

In the Therapeutic Studies population (N = 1493), 2,228 serious adverse events were reported (1.5/patient). The serious adverse events most frequently reported in the voriconazole patients and their relationship to treatment are listed in Table 8-35.

Table 8-35 Pooled Safety Database Most Frequently Reported Serious Adverse Events Occurring During Therapy or Within 30 Days of End of Therapy - Therapeutic Studies Population

Serious Adverse Event	**Voriconazole Therapeutic Studies (N = 1493)**	
	All causality n (%)#	**Treatment related* n (%)**
Sepsis	135 (9.0)	8 (0.5)
Pneumonia	102 (6.8)	5 (0.3)
Respiratory insufficiency	92 (6.2)	5 (0.3)
Dyspnea	77 (5.2)	5 (0.3)
Fever	71 (4.8)	0
Fungal infection	59 (4.0)	0
Acute granulocytic leukemia	58 (3.9)	1 (0.1)
Circulatory failure	56 (3.8)	4 (0.3)
Acute renal failure	53 (3.5)	15 (1.0)
Cardiac arrest	42 (2.8)	2 (0.1)

*Treatment-related by Sponsor or investigator. Relationship ascribed to study drug when a role for drug could not be ruled out or was one possible factor in a spectrum of causalities.
#It should be noted that this table includes 4 serious adverse events from two studies, Japanese Non-Comparative Fungal Infection Study (Deep-Seated Mycoses Study) and the Comparative Paracoccidioides Study (1010). Patients from these studies are not included in the denominators for these tables.

The most frequently reported all-causality serious adverse event in the Therapeutic Studies population was sepsis. The most frequently reported treatment-related serious adverse event in the Therapeutic Studies population was acute renal failure. Both of these adverse events are discussed in more detail below. A similar pattern of serious adverse events is seen in data from the Overall Pooled population.

Table 8-36 Pooled Safety Database – Most Frequently Reported Serious Adverse EventsOccurring During Therapy or Within 30 Days of End of Therapy – Overall Pooled Population

Serious Adverse Event	Voriconazole Overall Pooled (N = 2090)	
	All causality n (%)#	Treatment related n (%)[a]
Sepsis	245 (11.7)	17 (0.8)
Respiratory insufficiency	189 (9.0)	9 (0.4)
Pneumonia	184 (8.8)	9 (0.4)
Fever	148 (7.1)	2 (0.3)
Dyspnea	136 (6.5)	10 (0.5)
Fungal infection	117 (5.6)	1 (<0.1)
Acute granulocytic leukemia	101 (4.8)	3 (0.1)
Circulatory failure	93 (4.4)	7 (0.3)
Acute renal failure	87 (4.2)	22 (1.1)
Multi organ failure	65 (3.1)	13 (0.6)

*Treatment-related by Sponsor or investigator. Relationship ascribed to study drug when a role for drug could not be ruled out or was one possible factor in a spectrum of causalities
#It should be noted that this table includes 4 serious adverse events from two studies, Japanese Non-Comparative Deep-Seated Mycoses Study (1001) and the Comparative Paracoccidioides Study (1010). Patients from these studies are not included in the denominators for these tables.

8.7.1.4 Treatment Emergent Adverse Events

The most frequent treatment emergent all causality adverse events occurring in patients in the Therapeutic Studies population (N=1493) and the Overall Pooled population (N=2090) are listed in Table 8-37.

Table 8-37 Pooled Safety Database – Most Frequently Reported Adverse Events – Therapeutic Studies

Adverse Events*	Voriconazole Therapeutic Studies (N = 1493) n (%)	Voriconazole Overall Pooled (N = 2090) n (%)
Abnormal vision	358 (24.0)	422 (20.2)
Fever	324 (21.7)	430 (20.6)
Rash	268 (18.0)	362 (17.3)
Vomiting	259 (17.3)	327 (15.6)
Nausea	229 (15.3)	269 (12.9)
Diarrhea	215 (14.4)	282 (13.5)
Headache	191 (12.8)	233 (11.1)
Sepsis	175 (11.7)	259 (12.4)
Peripheral Edema	176 (11.8)	211 (10.1)
Respiratory Disorder	159 (10.6)	229 (11.0)

*Reported in ≥10% of voriconazole patients in either population

8.7.1.5 Conclusions

There was a similar pattern of adverse events in the pooled populations (Therapeutic Studies [N=1493] and Overall Pooled [N=2090]) compared with those reported in the large comparative trials.

8.7.2 Long Term Therapy

There were 304 of the 1946 patients who received voriconazole for greater than 84 days (12 weeks) in the November 2000 NDA (NDA Long-Term Voriconazole Therapy Population). No amphotericin B, liposomal amphotericin B, or fluconazole patients received treatment for longer than 84 days. Adverse events that occurred for the first time or increased in severity on or after Day 85 of voriconazole use are reviewed in this section. Data from the NDA All Voriconazole population are presented for reference.

The median duration of therapy in the NDA Long-Term Voriconazole Therapy population was 163 days, whereas the median duration of therapy for the NDA All Voriconazole Population was 14 days (Table 8-38). NDA Long-Term Voriconazole Therapy patients received voriconazole for up to 1014 days.

Table 8-38 Pooled Safety Database - Duration of Therapy - NDA Long-Term Voriconazole Therapy Population and NDA All Voriconazole Population

Duration of Treatment (days)	NDA Long-term Voriconazole Therapy (N = 304)	NDA All Voriconazole (N= 1946)
Median	163	14
n (%) patients receiving randomized treatment for:		
≤14 days therapy	N/A	1065 (54.7)
>14 days therapy	N/A	881 (45.3)
>28 days therapy	N/A	553 (28.4)
>84 days therapy	304 (100.0)	304 (15.6)
>180 days therapy	117 (38.5)	117 (6.0)
>365 days therapy	17 (5.6)	17 (0.9)

Discontinuations presented for patients in the NDA Long-Term Voriconazole Therapy Population are those that occurred after 84 days of therapy. Adverse events leading to the discontinuation of more than one patient in the NDA Long-Term Voriconazole Therapy Population are shown in Table 8-39.

Table 8-39 Pooled Safety Database - Adverse Events Leading to Discontinuation – NDA Long-Term Voriconazole Therapy Population and NDA All Voriconazole Population

	NDA Long-Term Voriconazole Therapy (N=304) n (%)	NDA All Voriconazole (N=1946) n (%)
Patients with adverse events	289 (95.1)	1694 (87.1)
Patients discontinued due to adverse events	27 (8.9)	259 (13.3)
Adverse event leading to discontinuation		
Abnormal liver function tests	3 (1.0)	13 (0.7)
Fever	2 (0.7)	5 (0.3)
Increased alkaline phosphatase	2 (0.7)	27 (1.4)
Increased hepatic enzymes	2 (0.7)	19 (1.0)
Rash	2 (0.7)	14 (0.7)

Thirty-three of the 304 NDA Long-Term Voriconazole Therapy Population died (10.8%) during treatment or within 30 days after the end of treatment. The causes of death occurring in more than one subject were septicemia (3), respiratory failure (3), acute lymphoid leukemia (2), acute myelocytic leukemia (2), unspecified leukemia (2), aspergillosis (2), complications of transplanted bone marrow (2), other diseases of lung (2) and heart failure (2).

The most frequent serious adverse events reported in ≥2% of patients in the NDA Long-Term Voriconazole Therapy group are summarized in Table 8-40.

Table 8-40 Pooled Safety Database - Most Frequently Reported Serious Adverse Events Occurring During Therapy or Within 30 Days of End of Therapy – NDA Long-Term Voriconazole Therapy Population and NDA All Voriconazole Population

	NDA Long-Term Voriconazole Therapy (N=304) n (%)	NDA All Voriconazole (N=1946) n (%)
Patients with serious adverse events	143 (47.0)	882 (45.3)
Serious adverse events		
Fever	28 (9.2)	81 (4.2)
Sepsis	22 (7.2)	149 (7.6)
Pneumonia	20 (6.6)	101 (5.2)
Acute granulocytic leukemia	12 (3.9)	58 (3.0)
Respiratory insufficiency	10 (3.3)	98 (5.0)
Fungal infection	8 (2.6)	76 (3.9)
Dyspnea	8 (2.6)	76 (3.9)
Graft *vs.* host disease	8 (2.6)	39 (2.0)
Medical procedure	8 (2.6)	35 (1.8)
Cardiac failure	6 (2.0)	29 (1.5)
Convulsions	6 (2.0)	21 (1.1)
Transplant rejection /complication	6 (2.0)	16 (0.8)
Appl/inj/incision/insertion site infection/inflammation	6 (2.0)	14 (0.7)

The most frequent treatment emergent all causality adverse events reported by > 5% of patients in the NDA Long-Term Therapy Voriconazole Population are summarized in Table 8-41.

Table 8-41 Pooled Safety Database - Most Frequent Adverse Events - Long-Term Voriconazole Therapy Population and NDA All Voriconazole Population

Adverse Event	NDA Long-Term Voriconazole Therapy (N=304) n (%)	NDA All Voriconazole (N=1946) n (%)
Number with adverse events	221 (72.7)	1691 (86.9)
Adverse events		
Rash	35 (11.5)	282 (14.5)
Fever	30 (9.9)	325 (16.7)
Pneumonia	25 (8.2)	144 (7.4)
Diarrhea	25 (8.2)	212 (10.9)
Sepsis	22 (7.2)	176 (9.0)
Cough increased	21 (6.9)	104 (5.3)
Abdominal pain	20 (6.6)	169 (8.7)
Respiratory tract infection	17 (5.6)	98 (5.0)
Respiratory disorder	17 (5.6)	158 (8.1)
Vomiting	17 (5.6)	247 (12.7)
Photosensitivity reaction	17 (5.6)	28 (1.4)

Photosensitivity reactions, pneumonia, and cough increased occurred more frequently in the Long-Term Voriconazole Therapy population than in the NDA All Voriconazole population.

8.7.3 Pediatric Patients

Experience of voriconazole use in children is based on two pharmacokinetic studies conducted in immunocompromised children and on safety data collected in the compassionate use programs. There were 52/1946 patients aged under 12 in the November 2000 NDA (NDA All Voriconazole population). One of these patients was enrolled into the NDA Therapeutic Studies Population and the other 51 received voriconazole in the compassionate program.

The patient who was less than 12 years of age in the NDA Therapeutic Studies Population had three adverse events (rash, osteomalacia, and vomiting), but completed the study. The following discussion therefore refers to the 51 patients of less than 12 years in the compassionate use program.

Of the 51 patients, 35 were male (68.6%) and the majority were white (41/51, 80.4%). The duration of treatment is shown in Table 8-42.

Table 8-42 Pooled Safety Database - Duration of Therapy - NDA All Voriconazole Population – Patients Less than 12 Years

Duration of Treatment (days)	Patients <12 years (N=51) n (%)
Median duration	82
Number of patients receiving voriconazole for	
≤14 days therapy	11 (21.6)
>14 days therapy	40 (78.4)
>28 days therapy	36 (70.6)
>84 days therapy	24 (47.1)
>180 days therapy	20 (39.2)
>365 days therapy	6 (11.8)

Eighteen of 51 of <12 year old patients (35.3%) died. The most frequent cause of death was respiratory failure (7 patients).

Serious adverse events reported by more than two patients less than 12 years old were fever (10/51; 19.6%), sepsis (10/51; 19.6%), respiratory insufficiency (10/51; 19.6%), inflammation at the injection site (4/51; 7.8%), abscess (4/51; 7.8%), respiratory tract infection (4/51; 7.8%), acute renal failure (3/51; 5.9%), cellulitis (3/51; 5.9%), and pneumonia (3/51; 5.9%).

Discontinuations due to adverse events in patients <12 years are shown in Table 8-43.

Table 8-43 Pooled Safety Database - Discontinuations due to Adverse Events - NDA All Voriconazole Population – Patients Less than 12 Years

	Patients < 12 years (N=51) n (%)
Number of patients with adverse events	44 (86.3)
Discontinued due to adverse events	6 (11.8)
Lab test abnormal	1 (2.0)
Leukemia	1 (2.0)
Photosensitivity reaction	1 (2.0)
Cheilitis	1 (2.0)
Respiratory disorder	1 (2.0)
Respiratory tract infection	1 (2.0)
AST increased	1 (2.0)
ALT increased	1 (2.0)

ALT = alanine transaminase; AST = aspartate transaminase

No one adverse event led to the discontinuation of more than one patient.

All causality adverse events that occurred in four or more patients aged less than 12 years are displayed in Table 8-44.

Table 8-44 Pooled Safety Database - Adverse Events - NDA All Voriconazole Population – Patients Less than 12 Years

Adverse Events	**Patients < 12 years (N=51) n (%)**
Patients with adverse events	44 (86.3)
Adverse events	
Fever	13 (25.5)
Sepsis	10 (19.6)
Rash	9 (17.6)
Vomiting	7 (13.7)
Diarrhea	7 (13.7)
Pneumonia	7 (13.7)
Respiratory disorder	7 (13.7)
Herpes zoster	7 (13.7)
Abdominal pain	5 (9.8)
Abscess	5 (9.8)
Respiratory tract infection	5 (9.8)
Leukopenia	4 (7.8)
Photosensitivity reaction	4 (7.8)
Pharyngitis	4 (7.8)
Conjunctivitis	4 (7.8)
Acute kidney failure	4 (7.8)

An additional 39 patients less than 12 years (11 from the Single Dose Pediatric Study [249] and 28 from the Multiple Dose Pediatric Study [1007]) were enrolled into two pharmacokinetic studies. In the Multiple Dose Pediatric Study (1007), patients received eight days of intravenous voriconazole treatment.

In the Single Dose Pediatric Study (249), two patients experience serious adverse events, neither of which was considered to be related to treatment. Both patients received a single dose of voriconazole on Day 1. A four year old female experienced moderate neutropenia, mild pyrexia and moderate febrile neutropenia on Day 3 (post treatment events) for which she was hospitalized. A four-year old male experienced febrile neutropenia on Day 12 for which he was hospitalized. Both events resolved.

In the Multiple Dose Pediatric Study (1007), serious adverse events were reported for eight subjects and three subjects died during therapy or within 30 days of the end of therapy. No serious adverse events were considered to be due to voriconazole. These serious adverse events are listed below:

- An 11-year old female with serious adverse events of clonic seizure, progressive seizures, short term memory loss and confusion. This was a post-therapy event which resolved.
- A five-year old female with serious adverse events of meningitis, sepsis, respiratory insufficiency and cerebritis. These events started on the final day of treatment and the subject later died.
- A two-year old male with a serious adverse event of polymicrobial sepsis. This was a post therapy event (Day 8 post-therapy) which resolved.
- A three-year old female with serious adverse events of *Streptococcus viridans* bacteremia and persistent fever. The events started on Day 11 and resolved.
- A seven-year old female with serious adverse events of sepsis, respiratory distress, and pulmonary effusion. The events started on Day 3 and resolved.
- A three-year old female with serious adverse events of worsening subdural haematoma and resultant seizures, and central nervous system hemorrhage. The events started on Day 16 and the patient died on Day 17.
- A four-year old male with a serious adverse event of cardiorespiratory arrest. This was a post therapy event and the subject later died.
- An eight-year old male with two serious adverse events. The first was typhlitis (neutropenic enterocolitis), and the second was acute febrile illness and neutropenia. These were all post-therapy events which resolved.

The 10 most commonly reported adverse events in the Multiple Dose Pediatric Study (1007) and all adverse events in the Single Dose Pediatric Study (249) are presented in Table 8-45.

Table 8-45 Multiple Dose Pediatric Study (1007) and Single Dose Pediatric Study (249) - Adverse Events

Adverse Event	Multiple Dose Pediatric Study (1007) (N = 28) n (%)	Single Dose Pediatric Study (249)	
		3 mg/kg IV (N = 6) n (%)	4 mg/kg IV (N = 5) n (%)
Vomiting	7	0	2
Sepsis	6	0	0
Diarrhea	6	0	1
Mucous membrane disorder	6	0	0
Fever	5	0	2
Abdominal pain	5	0	1
Epistaxis	5	0	0
Rash	4	0	2
Hypertension	4	0	0
Bilirubinemia	4	0	0
Pain	1	1	0
SGOT increased	0	1	0
Rhinitis	1	1	0
Leukopenia	2	0	1
Pruritis	2	0	1
Photophobia	1	0	1

Liver and renal related laboratory abnormalities from the multiple dose pharmacokinetic study in pediatric patients are shown in Table 8-46.

Table 8-46 Multiple Dose Pediatric Study (1007) - Liver and Renal Related Laboratory Abnormalities

Parameter	Criteria	Multiple Dose Pediatric Study (1007) (N = 28)	
		6 +3 mg/kg n (%)	4 mg/kg n (%)
Total bilirubin (mg/dl)	> 1.5 ULN	1/27 (3.7)	5/27 (18.5)
AST (IU/L)	> 3 ULN	1/27 (3.7)	1/27 (3.7)
ALT (IU/L)	> 3 ULN	2/27 (7.4)	3/27 (11.1)
Alkaline phosphatase (IU/L)	> 3 ULN	0/25 (0)	0/26 (0)
Serum creatinine (mg/dL)	> 1.3 ULN	0/26 (0)	0/27 (0)

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal

Overall, there were no serious adverse events or adverse events reported in the 51 patients less than 12 years old in the compassionate program of the NDA Overall Safety Population, or the 39 patients in the pharmacokinetic studies, that were not reported in adults.

8.7.4 Non-Therapeutic Studies

Two studies are included in the Non-Therapeutic Studies population. In the Dose Ranging Oropharyngeal Candidiasis Study (302), 167 patients were treated with oral voriconazole for seven days, at doses of 50 mg once daily (n = 53), 200 mg once daily (n = 58), or 200 mg bid (n = 56). In the Multiple Dose Adult Patient Pharmacokinetic Study (673), 18 patients with leukemia were treated with voriconazole for seven days, at doses of 200 mg bid (n = 9) and 300 mg bid (n = 9).

There were two deaths (1.1%) in this group (one bronchopneumonia and one meningoencephalitis due to toxoplasmosis) and 36 patients (19.5%) had one or more serious adverse event. Table 8-47 shows the most frequent serious adverse events in the Non-Therapeutic Studies population.

Table 8-47 Pooled Safety Database – Most Frequently Reported Serious Adverse Events Occurring During Therapy or Within 30 Days of End of Therapy - Non-Therapeutic Studies Population

Serious adverse event	Voriconazole Non-Therapeutic Studies (N = 185) n (%)
AIDS	9 (4.9)
Bacterial infection	4 (2.2)
Encephalopathy	3 (1.6)
Fever	3 (1.6)
Pneumonia	3 (1.6)
Respiratory disorder	3 (1.6)
Retinitis	2 (1.1)
Pneumocystis carinii infection	2 (1.1)

The most frequent serious adverse event was AIDS, the underlying disease of patients in the Dose Ranging Oropharyngeal Study (302). The most frequent adverse event in the Non-Therapeutic Studies and discontinuation due to these adverse events is shown in Table 8-48.

Table 8-48 Pooled Safety Database - Most Frequent Adverse Events and Reasons for Discontinuation due to Adverse Events – Non-Therapeutic Studies

Adverse Event	Voriconazole Non-Therapeutic Studies (N = 185)	
	Total n (%)	Leading to discontinuation n (%)
Abnormal vision	25 (13.5)	2 (1.1)
Headache	12 (6.5)	3 (1.6)
Diarrhea	11 (5.9)	2 (1.1)
Nausea	11 (5.9)	1 (0.5)
Vomiting	10 (5.4)	3 (1.6)
Rash	5 (2.7)	2 (1.1)
Myalgia	4 (2.2)	0
Fever	4 (2.2)	0

Abnormal vision was the most frequently reported adverse event in the non-therapeutic studies group.

8.8 Specific Safety Considerations

The following sections discuss specific safety issues of particular relevance to the use of voriconazole. In addition to the pooled populations discussed in the previous sections and outlined in Table 8-1, several datasets included in the Nov. 2000 NDA pooled safety databases are discussed in the following sections.

8.8.1 Visual Disturbances

8.8.1.1 Visual Disturbances as Adverse Events

Reports of visual disturbances on voriconazole treatment can generally be classified into four distinct categories (altered/enhanced visual perception, blurred vision, color vision change and photophobia). In the original NDA (November 2000), the most frequently reported description of visual disturbance was altered or enhanced visual perception (Table 8-49).

Table 8-49 Occurrence of Visual Disturbances by Each Event

Category	NDA Phase I Visual Disturbance Dataset* (N = 686)	NDA All Voriconazole Visual Disturbance Dataset* (N = 2343)
Total visual events	920	1748
Altered or enhanced visual perception	352 (38.3%)	563 (32.2%)
Blurred	129 (14.0%)	263 (15.0%)
Photophobia	252 (27.4%)	308 (17.6%)
Color vision change	46 (5.0%)	86 (4.9%)
Other	141 (15.3%)	528 (30.2%)

The visual disturbances appear to be transient with an approximate onset of 15-30 minutes after initiation of intravenous or oral dosing and an approximate duration of 30 minutes. The visual disturbances are infrequently associated with discontinuation of therapy. In the Overall Pooled population 11/2090 patients (0.5%) discontinued due to abnormal vision.

8.8.1.2 Effects of Voriconazole on the Retina

Mechanistic approaches show that the site of voriconazole's action is most likely within the retina, since the principal effects in both humans and dogs was a reduction in the amplitude of the electroretinogram (ERG) waveform (both a and b waves). Reductions in the amplitude and implicit time of the a wave of the ERG and reductions in the amplitude and slope of the b wave were noted in dog studies with voriconazole plasma concentrations similar to those observed in human volunteers; the magnitude of the reductions was proportional to the plasma concentration. Although ERG changes were observed in dogs, there were no morphometric, morphological or histological changes in the eye or retina in the long term dog toxicology studies (12 months duration of dosing) to suggest that any irreversible damage or degeneration had occurred.

The voriconazole effect on the ERG has also been studied in human beings. Results of the Single Dose Visual Function Study (231) demonstrated decreased amplitude of both the scotopic and photopic ERG waveform. This was characterized by a decline in both b1 and b2 wave amplitudes. The effect was more clear under scotopic conditions. However, the results also showed an effect on the cone system, *i.e.* under photopic conditions. Thus, voriconazole impaired both photoreceptor retinal systems, the cones and particularly the rods, during photopic and particularly during scotopic measures. As a result of these findings in the single dose study, the effects of voriconazole on the ERG, including reversibility, were examined in the Multiple Dose Visual Function Study (1004), in which patients were administered a loading dose of oral voriconazole 400 mg q 12 h x two doses, followed by 300 mg q 12 h for 28 days, or placebo. Details of this study are provided in Appendix 5. For the ERG results, 17 subjects were evaluable in each group. Voriconazole treatment resulted in statistically significant decreases in b wave amplitude at Step 2 and oscillatory potential amplitude at Step 3 on Day 29 compared with placebo. These effects were not present on Day 43, 14 days after the last dose. No statistically significant differences were seen for b wave amplitude at Steps 1 or 4, or flicker response amplitude at Step 5 on Day 29 compared with placebo. However, a treatment effect was noted in the flicker response amplitude at Step 5 on Days 1 and 8, but this was not present on Day 29.

The treatment comparisons for the ERG amplitude data are summarized in Table 8-50 for each Step and each day (evaluable subject population). The Day 43 results are presented only when a treatment difference existed on Day 29.

Table 8-50 Multiple Dose Visual Function Study (1004) - Results of ERG Amplitude Data

Variable	Study Day	Adjusted mean		Mean Difference	95% CI for Difference
		Voriconazole (n=17*)	Placebo (n=17*)		
b wave amplitude (microV) following a dim white light (0.001cd-s/m^2) flash in scotopic conditions	1	117.3	125.4	-8.1	-31.9,15.8
	8	116.2	121.6 (n=16)	-5.4	-27.5,16.7
	29	118.3	129.8	-11.5	-38.2,15.2
b wave amplitude (microV) following a white stimulus (1.5 to 3cd-s/m^2) in scotopic conditions	1	379.0	436.4	-57.4	-99.9,-14.8
	8	382.8	444.6	-61.8	-113.3,-10.3
	29	377.4	452.1 (n=16)	-74.7	-121.2,-28.2
	43	443.3	456.1	-12.8	-49.5,23.9
Oscillatory potential amplitude (microV) following a flash (1.5 to 3cd-s/m^2) repeated every 15 seconds (75 to 100Hz electronic low pass filter) in scotopic conditions	1	35.3	43.7	-8.4	-17.9,1.1
	8	38.1 (n=16)	45.5	-7.4	-14.7,-0.1
	29	30.4	47.6	-17.2	-24.4,-10.1
	43	44.6	41.5	3.1	-7.6,13.8
b wave amplitude (microV) following a single flash (1.5 to 3cd-s/m^2) in photopic conditions	1	40.8	45.7	-4.9	-11.4,1.6
	8	45.6	43.6	2.0	-5.6,9.5
	29	45.0	45.6	-0.6	-9.5,8.3
Flicker response amplitude (microV) using a 30Hz flicker (1.5 to 3cd-s/m^2) in photopic conditions	1	57.5	76.6	-19.1	-27.1,-11.0
	8	58.6 (n=16)	77.0	-18.4	-27.4,-9.5
	29	64.9	68.2	-3.3	-16.5,9.9

CI = 95% confidence interval
*n=17 unless otherwise specified in parentheses.

Due to technical difficulties, the results of the scotopic dim flash and the photopic b wave amplitude assessment are unreliable. The results of the scotopic b-wave amplitude are robust, however. These results show that the decrease of the ERG waveform amplitude caused by voriconazole occurs after a single day of treatment, but does not progress further and is fully reversible after discontinuation of treatment.

In the Farnsworth-Munsell 100 hue test there was an increase in error score in the voriconazole treated volunteers for the blue-green caps on Days 3 and 7, but scores were similar to baseline by Day 28. Placebo volunteers had decreasing error scores as the study progressed (this may be a result of a learning effect) and error scores were lower than on voriconazole on Day 28.

In the Humphrey visual field test reductions in mean deviation and increases in pattern standard deviation and short-term fluctuation were observed with both eyes in the voriconazole treated group on Days 3 and 7. Mean values were returning to baseline on Day 28 and were similar to baseline on Day 42.

There were no reports of abnormalities with the slit lamp test, external eye test or funduscopy (direct and indirect).

Although there are no morphological data in humans, the retinal effect in the human ERG studies occurred at plasma concentrations comparable to those observed in the dog ERG study. These plasma concentrations were also similar to those measured in the dog toxicology studies, where no retinal morphological changes were detected.

8.8.1.3 Visual Function Testing in the Clinical Studies

The risks to the eyesight of patients given voriconazole were assessed in functional visual tests, appropriate for the patient population involved. More rigorous visual function assessment was performed in volunteer and selected patient trials. In the Esophageal Candidiasis Study (305) visual acuity, funduscopy, color vision testing and contrast sensitivity were performed. For visual acuity and contrast sensitivity approximately 50% of patients in both groups had no change; the majority of changes observed were not clinically significant and similar numbers of patients improved and deteriorated in the two treatment groups. For color perception,124 of 200 voriconazole patients (62.0 %) and 135 of 191 fluconazole patients (70.7%) had no change. For funduscopy, few patients in either group who had normal baseline fundus examinations showed any deterioration after treatment. The only functional test that showed any change was an alteration of color perception, as reported above for Study 1004. In contrast, the poor condition of the patients treated in the Phase 3 studies did not generally allow rigorous testing.

8.8.1.4 Incidence in Patient Subpopulations

With two exceptions, no apparent influence of gender, race, age or weight on the incidence of visual disturbances was suggested, with rates of abnormal vision in these subpopulations between 30 and 40%. Of patients aged 12-15 years in the original NDA Therapeutic Studies dataset (total n = 1214), 11/20 (55%) reported visual disturbances. Twelve of 12 subjects (100%) aged ≥75 years in the voriconazole clinical pharmacology studies reported visual disturbances. The latter were entered in the Male/Female and Young/Elderly Study (250), and were exposed to relatively high concentrations of voriconazole and experienced a higher incidence of all adverse events, including visual effects. When the original NDA Therapeutic Studies population (n = 1214) is examined, visual disturbances do not appear to be reported any more frequently in the 75 years and older age group (4/22,18.2%) than in patients aged 16-44 years (193/586, 32.9%) or in patients aged 45-64 years (154/473, 32.6%).

The incidence of visual disturbances in various subpopulations with underlying retinal disease was examined to determine if these patients were more susceptible to the visual effects of voriconazole. Even before developing overt retinopathy, diabetic patients have an early loss of short wavelength cone sensitivity. Patients with retinitis, due either to *Cytomegalovirus* infection or to cytotoxic chemotherapies, were treated with voriconazole. There were 156 patients who received voriconazole and had baseline conditions (diabetes, *Cytomegalovirus* retinitis, other retinitis) where a higher susceptibility to visual disturbance may have been anticipated. These subjects did not report visual disturbances at a rate higher than other Phase 2/3 subjects, as demonstrated in Table 8-51, which presents the frequency of visual disturbances in patients included in the NDA All Voriconazole population (n = 1946) in patients with various underlying conditions.

Table 8-51 Frequency of Visual Disturbances in Voriconazole Patients with Baseline Ocular Complications – NDA All Voriconazole Population

	NDA All Voriconazole (N = 1946)
Baseline condition	Rate of visual disturbance n/N (%)
Diabetes	32/124 (25.8)
Cytomegalovirus retinitis	6/18 (33.3)
Other retinitis	9/31 (29.0)
Total	42/156 (26.9)

In summary, although visual disturbances occur frequently on voriconazole, few patients discontinue therapy as a result and there is no evidence of a long term impact on retinal structure, as assessed by animal toxicology studies (up to two years in rats and mice and one year in dogs). The effects on the electroretinogram in humans observed over 28 days of treatment are fully reversible within two weeks of discontinuation. Although the mechanism remains unclear, the site of action is within the retina and both rod and cone pathways appear to be affected.

8.8.2 Hepatic Function

Hepatic function test abnormalities tend to be reported at high rates in clinical trials of antifungal agents, regardless of whether an azole or polyene is being studied. Table 1 in Appendix 6 presents literature information on the frequency of hepatic function test abnormalities in clinical trials of antifungal agents, either as treatment of mycoses or as prophylaxis/empirical therapy.

The liver was identified as the target organ during the toxicology program. Review of the hepatic function test abnormalities occurring in voriconazole-treated patients shows a frequency of abnormalities similar to those reported in the literature with other antifungal drugs. Data from the 3 large comparative Phase 3 trials allows direct comparison of voriconazole to amphotericin B + Other Licensed Antifungal Therapy (in the randomized open label Global Comparative Aspergillosis Study [307/602]), to liposomal amphotericin B (in the Empirical Therapy Study [603]), and to fluconazole (in the Esophageal Candidiasis Study [305]).

Table 8-52 presents the occurrences of clinically significant hepatic function test abnormalities in the Global Comparative Aspergillosis Study (307/602).

Table 8-52 Global Comparative Aspergillosis Study (307/602) - Occurrence of Clinically Significant Hepatic Function Test Abnormalities – Safety Population

Clinically Significant Hepatic Function Test Abnormalities	Hepatic Laboratory Parameter	Voriconazole (N = 196) n (%)	Amphotericin B/OLAT (N = 185) n (%)
Without regard to baseline*	Total bilirubin	35/180 (19.4)	46/173 (26.6)
	AST	21/180 (11.7)	18/174 (10.3)
	ALT	34/180 (18.9)	40/173 (23.1)
	Alkaline Phosphatase	29/181 (16.0)	38/173 (22.0)
With normal baseline*	Total bilirubin	13/135 (9.6)	29/148 (19.6)
	AST	15/147 (10.2)	9/136 (6.6)
	ALT	18/120 (15.0)	20/115 (17.4)
	Alkaline Phosphatase	8/114 (7.0)	17/118 (14.4)
With abnormal baseline**	Total bilirubin	7/45 (15.6)	11/25 (44.0)
	AST	4/33 (12.1)	8/38 (21.1)
	ALT	11/60 (18.3)	13/58 (22.4)
	Alkaline Phosphatase	17/67 (25.4)	19/55 (34.5)

ALT = alanine transaminase; AST = aspartate transaminase; OLAT = Other Licensed Antifungal Therapy
*Clinically significant defined as: total bilirubin mg/dL > 1.5 x ULN; AST, ALT, alkaline phosphatase IU/ L > 3 x ULN
**Clinically significant defined as: total bilirubin, AST, ALT, alkaline phosphatase > 1.5 x baseline

Hepatic function test abnormalities, when assessed without regard to baseline, with a normal baseline, or with an abnormal baseline, either showed a similar or lower frequency of occurrence in the voriconazole-treated patients compared with the amphotericin B + Other Licensed Antifungal Therapy–treated patients.

Table 8-53 presents the occurrences of clinically significant hepatic function test abnormalities in the Empirical Therapy Study (603/MSG42)

Table 8-53 Empirical Therapy Study (603/MSG42) - Occurrence of Clinically Significant Hepatic Function Test Abnormalities – Intention to Treat Population

Clinically Significant Hepatic Function Test Abnormalities	Hepatic Laboratory Parameter	Voriconazole (N = 421) n (%)	Liposomal amphotericin B (N = 428) n (%)
Without regard to baseline*	Bilirubin	106/400 (26.5)	128/393 (32.6)
	AST	22/396 (5.6)	17/393 (4.3)
	ALT	30/385 (7.8)	25/374 (6.7)
	Alkaline phosphatase	27/399 (6.8)	26/394 (6.6)
With normal baseline*	Bilirubin	33/282 (11.7)	48/276 (17.4)
	AST	15/364 (4.1)	14/363 (3.9)
	ALT	18/330 (5.5)	18/318 (5.7)
	Alkaline phosphatase	10/317 (3.2)	14/326 (4.3)
With abnormal baseline**	Bilirubin	36/118 (30.5)	42/117 (35.9)
	AST	5/32 (15.6)	3/30 (10.0)
	ALT	7/55 (12.7)	7/56 (12.5)
	Alkaline Phosphatase	12/82 (14.6)	9/68 (13.2)

ALT = alanine transaminase; AST = aspartate transaminase
*Clinically significant defined as: total bilirubin mg/dL > 1.5 x ULN; AST, ALT, alkaline phosphatase IU/ L > 3 x ULN
**Clinically significant defined as: total bilirubin, AST, ALT, alkaline phosphatase > 1.5 x baseline

Hepatic function test abnormalities when assessed without regard to baseline, with a normal baseline, or with an abnormal baseline, showed a similar frequency of occurrence in the voriconazole-treated patients compared with the liposomal amphotericin B–treated patients.

Table 8-54 presents the occurrences of clinically significant hepatic function test abnormalities in the Esophageal Candidiasis Study (305).

Table 8-54 Esophageal Candidiasis Study (305) - Occurrence of Clinically Significant Hepatic Function Test Abnormalities – Intention to Treat Population

Clinically Significant Hepatic Function Test Abnormalities	Hepatic Laboratory Parameter	Voriconazole (N = 200) n (%)	Fluconazole (N = 191) n (%)
Without regard to baseline*	Bilirubin	8/185 (4.3)	7/186 (3.8)
	AST	38/187 (20.3)	15/186 (8.1)
	ALT	20/187 (10.7)	12/186 (6.5)
	Alkaline Phosphatase	19/187 (10.2)	14/186 (7.5)
With normal baseline*	Bilirubin	4/174 (2.3)	5/179 (2.8)
	AST	7/93 (7.5)	3/102 (2.9)
	ALT	8/119 (6.7)	4/139 (2.9)
	Alkaline Phosphatase	7/128 (5.5)	3/140 (2.1)
With abnormal baseline**	Bilirubin	0/11	0/7
	AST	24/94 (25.5)	9/84 (10.7)
	ALT	7/68 (10.3)	6/47 (12.8)
	Alkaline Phosphatase	9/59 (15.3)	4/46 (8.7)

ALT = alanine transaminase; AST = aspartate transaminase
*Clinically significant defined as: total bilirubin mg/dL > 1.5 x ULN; AST, ALT, alkaline phosphatase IU/ L > 3 x ULN
**Clinically significant defined as: total bilirubin, AST, ALT, alkaline phosphatase > 1.5 x baseline

Hepatic function test abnormalities when assessed without regard to baseline, with a normal baseline, or with an abnormal baseline, showed a higher frequency of occurrence in the voriconazole-treated patients compared with the fluconazole–treated patients.

In Phase 1 studies, in healthy volunteers, there were rare occurrences of clinically-significant hepatic function test abnormalities. Importantly, in the three healthy volunteers who had clinically significant hepatic function test abnormalities in the Multiple Dose Escalation IV/Oral Switch Study (230), the values returned to normal soon after voriconazole discontinuation.

Overall review of the data supports an occurrence of hepatic function test abnormalities in voriconazole-treated patients that is greater than placebo (in normal volunteers), greater than fluconazole (in patients with esophageal candidiasis), but similar to the occurrence of hepatic function test abnormalities in patients receiving liposomal amphotericin B (as empirical therapy) or amphotericin B + Other Licensed Antifungal Therapy (as treatment of acute, invasive aspergillosis). A comparison with literature information in equivalent, severely ill, populations, also does not suggest a greater risk of hepatotoxic reactions with voriconazole compared with other antifungal therapies.

In the overall voriconazole development program, there were 26 reports of hepatic failure of all etiologies, 19/2090 (0.9%) receiving voriconazole and 7/856 (0.8%) receiving active comparator (Table 8-55).

Table 8-55 Summary of Patients with Hepatic Failure in the Overall Pooled Population

PID	Gender	Age (yr)	Duration Rx (day)	DOD	Clinical Event	Causality (Investigator Assessed)
Voriconazole (N = 2090)						
303A/0603	M	33	39	69	Anemia, GI bleed, hepatic failure	Other illness (GI ulcer)
304/0736	M	51	5	44	Hypoglycemia, ARDS, hemorrhage, hepatic failure, renal failure, cirrhosis – bled on liver biopsy	Study drug
304/0333	M	44	11	11	Progression of AIDS, hepatic failure	Other illness (AIDS, cirrhosis)
309/1487	M	64	19	40	Hepatic failure, renal dysfunction, cardiac failure, sepsis, anemia, apnea	Other illness (graft *vs.* host disease, hypoperfusion, sepsis), possible contribution by study drug
603/4096	M	43	8	15	Organic brain syndrome, septicemia, renal failure, hepatic failure	Other (disease under study, septicemia)
603/0351	M	48	11	41	Hemorrhagic cystitis, acute renal failure, graft *vs* host disease, hepatic failure, MI	Other (cyclophosphamide, graft *vs,* host disease, bone marrow transplant)
603/0176	M	36	17	42	Acute renal failure, pulmonary edema, respiratory failure, thrombocytopenia, multiple organ failure, hepatic failure	Concomitant treatment (chemotherapy, amphotericin B, cyclosporine, antibiotics)
603/0369	M	49	9	9	Pulmonary failure, renal failure, multiple organ failure, adult respiratory distress syndrome, hepatic failure	Other (total body irradiation, chemotherapy)
603/1340	M	39	2	17	Progression of acute myelocytic leukemia, hepatic failure, renal failure, respiratory failure, multiorgan failure	Other illness (progression of acute myelocytic leukemia)
604/6244	F	61	3	54	Worsening renal insufficiency, hepatic failure, chronic myelocytic leukemia	Other (cyclosporine, antibiotics, bone marrow transplant, graft vs host disease)
604/6168	M	13	171	175	Urinary tract infection, pneumonia, graft *vs* host disease, hepatic failure, fungemia	Other illness (bone marrow transplant)

PID	Gender	Age (yr)	Duration Rx (day)	DOD	Clinical Event	Causality (Investigator Assessed)
604/6035	M	23	5	25	Respiratory distress, intermittent supraventricular tachycardia, acute renal dysfunction, sepsis, progression of acute myelocytic leukemia, hepatic failure	Other (Aspergillosis, acute myelocytic leukemia)
606/0131	M	17	34	42	Worsening hyperbilirubinemia, hepatic failure, pulmonary failure, *Cytomegalovirus* pneumonitis	Graft *vs.* host disease, association with study drug possible
606/0330	F	16	54	54	ARDS, progression of hepatic failure, progression of renal failure, graft *vs.* host disease	Other illness (hepatic failure due to graft *vs.* host disease)
606/0318	M	60	6	7	Progression of hepatic failure, brain abscess, respiratory failure, hepatitis C, subdural hematoma, renal failure, coagulopathy	Disease under study (invasive mycoses)
606/0209	M	37	21	28	Elevated bilirubin, elevated creatinine, pericarditis, pulmonary effusion, respiratory distress, hepatic failure	Other illness (venous occlusive disease, volume overload)
607/6066	F	37	257	323	Femoral vein thrombosis, exacerbation of hyperbilirubinemia and systemic lupus erythematosus, elevated transaminases, hepatic failure	Study drug may have contributed
608/0031	F	76	18	18	Sepsis, hepatic failure, worsening renal insufficiency, adult respiratory distress syndrome, pulmonary failure, multiple organ system failure	Other (perforated colon, pneumonia, sepsis)
1025297-1	M	35	75	75	Acute hepatic and renal failure	Other illness (AIDS, hepatitis, alcohol abuse)
Active Comparator (N = 856) (Note: All 7 cases were in patients receiving Amphotericin B)						
307/0153	M	50	21	30	Progression of non-Hodgkins lymphoma, hepatic failure, septicemia	Other (non-Hodgkins lymphoma, disease under study)
603/0041	M	51	8	26	Hepatic failure, graft *vs.* host disease,	Other (bone marrow transplant, graft vs host disease)

PID	Gender	Age (yr)	Duration Rx (day)	DOD	Clinical Event	Causality (Investigator Assessed)
603/0444	M	49	1	3	Pulmonary failure, acute renal failure, septicemia, septic shock, multiorgan failure	Other illness (immunosupression, septicemia)
603/1279	F	23	10	11	Fungal sepsis, hepatic failure, recurrent respiratory failure, renal failure, cardiac failure, septic shock, adult respiratory distress syndrome, multiorgan failure	Other illness (disseminated aspergillosis, T-cell lymphoma)
603/2520	F	32	6	16	Septic shock, disseminated intravascular coagulopathy, , respiratory failure, progression of leukemia, hepatic failure	Other (underlying disease, chemotherapy, septic shock, *Pseudomonas*)
603/2798	F	50	63	64	Renal failure, respiratory failure, hepatic failure, progressive sepsis, intracranial hemorrhage	Other (fluid overload, renal failure, Cytoxan, cyclosporine, sepsis, pneumonia, cytopenia)
608/0068	M	42	1	2	Hepatic failure, renal failure, heart failure, lung failure, multiorgan failure	Disease under study (candidemia)

*DOD = day of death

Among these 26 cases of hepatic failure, there were four deaths following voriconazole which were potentially related to treatment according to either the investigator or the Sponsor. The case histories of these four patients are summarized below:

- Patient 606/0131 was a 17 year old male with a history of acute myelocytic leukemia status-post allogeneic bone marrow transplant complicated with graft vs. host disease of skin, gastrointestinal tract and liver who developed pulmonary cryptococcosis which failed to respond to other therapy (amphotericin B). The patient was started on compassionate use voriconazole and treated for 35 days and died seven days after the end of therapy. The investigator attributed death to *Cytomegalovirus* pneumonitis, hepatic failure and pulmonary failure. The final autopsy report attributed the cause of death to progressive hepatic and pulmonary failure. Autopsy findings included moderate hepatic graft *vs.* host disease of the liver, with severe cholestasis and periportal fibrosis, extensive fibrosis of the liver consistent with a history of chemotherapy, severe diffuse alveolar damage, bilateral focal *Cytomegalovirus* pneumonitis and umbilical cord blood transplant.
- Patient 304/0736 was a 51year old male with type II diabetes mellitus, undiagnosed cirrhosis and acute invasive aspergillosis of the orbit. He was treated for seven days with itraconazole, then was started on voriconazole in the Non-Comparative Aspergillus Study (304). On day 4 of voriconazole, the patient became confused and hypoglycemic and the voriconazole was discontinued. These symptoms resolved but he had residual fever and dyspnea resulting in a diagnosis of pneumonia. On day 6, the patient required intubation.

Amphotericin B colloidal dispersion 250 mg daily was started (Day 9) for 26 days. His course was complicated by the persistent need for ventilatory support. Hepatosplenomegaly was noted on day 38. Further work-up ensued and a liver biopsy was performed on day 43 with subsequent intraperitoneal hemorrhage and death. The biopsy showed active cirrhosis. The patient was subsequently found to have an undisclosed history of alcohol abuse. Autopsy results attributed the patient's death to intraperitoneal hemorrhage and adult respiratory distress syndrome. The investigator attributed the hepatic failure and death as related to voriconazole.

- Patient 607/6066 was a 37 year old female with autoimmune hemolytic anemia associated with underlying systemic lupus erythematosis, who received voriconazole for the extended treatment of central nervous system aspergillosis. The patient entered Study 607 as a continuation of treatment received in Study 604. On day 210, the patient was admitted to the hospital with a one week history of left lower extremity edema and was diagnosed with common femoral vein thrombosis. An arteriogram showed a left femoral clot around the area of her arteriovenous fistula which was used for hemodialysis. The patient was treated with enoxaparine. On day 212, the patient developed an exacerbation of her lupus and was treated with intravenous methylprednisolone. On day 257, voriconazole was temporarily discontinued due to a sustained elevation in aspartate transaminase (AST) and alanine transaminase (ALT). On day 305, 49 days after the discontinuation of voriconazole, the patient was hospitalized for symptoms of worsening fatigue, chills without fever, right sided pleuritic chest pain, and increasing abdominal girth and was diagnosed with liver failure. She requested no further invasive or resuscitative procedures be performed and died 67 days after the last dose of voriconazole. The investigator attributed the hypertransaminasemia and progressive liver failure (cause of death) to voriconazole. Review by the Sponsor attributed the hypertransaminasemia and progressive liver failure to the patient's chronic active autoimmune hepatitis and SLE; however, a causal relation to voriconazole could not be excluded.
- Patient 309/1487 was a 64 year old male with underlying non-Hodgkin's lymphoma. He had had an allogeneic bone marrow transplant, complicated by Graft *vs.* Host Disease and received voriconazole for refractory hepatic aspergillosis. Liver function test values were elevated at baseline. He had previously been treated with other antifungal agents: fluconazole (400mg daily), conventional amphotericin B (90mg daily) and liposomal amphotericin B (180mg daily). He received voriconazole for 19 days but was discontinued due to the onset of renal and hepatic failure. On day 27 a liver biopsy showed massive cholestasis, necrosis, Graft *vs.* Host Disease, no inflammation, vasculitis or evidence of fungal infection. On Day 40, the patient died from *E. faecalis* sepsis and hepatic and cardiac failure. In the opinion of the investigator, the cause of death was hepatic failure secondary to Graft *vs.* Host Disease, although a possible contribution of hepatic fungal infection or study drug could not be ruled out.

In conclusion, the review of hepatic function test abnormalities and patients of hepatic failure suggests that hepatic adverse events occur in patients treated with voriconazole at a frequency comparable to that seen in those given amphotericin B and liposomal amphotericin B, although at a greater frequency than that of fluconazole. Data suggest that hepatic function test abnormalities occurring with voriconazole are reversible following dose reductions or withdrawal of the drug. Nevertheless, prescribing physicians should be made fully aware of this important potential side effect associated with the use of voriconazole and it is recommended that hepatic function (including transaminases and bilirubin) be routinely monitored in patients receiving voriconazole. Should elevations in hepatic function tests be found, the patient should be monitored for signs and symptoms of hepatic failure, and discontinuation of voriconazole should be considered if a causal association is suspected. These recommendations are the same as those provided to investigators in the voriconazole clinical program. After the New Drug Application was filed, an independent expert panel of hepatologists performed a blinded review of all cases of hepatic failure leading to death. The panel determined that one case could be potentially related to voriconazole treatment.

8.8.3 Skin Reactions

Skin rash was observed in 278/1493 (18.6%) voriconazole patients in the Therapeutic Studies population and 362/2090 (17.3%) voriconazole patients in the Overall Pooled population. Table 8-56 shows the frequency of rash reported as an adverse event in the pooled safety database populations Therapeutic Studies and Overall Pooled and in the Phase 3 Comparative Studies. The preferred term 'rash' includes event terms such as erythema, erythamtous rash, exanthema, redness, and less specific terms such as rash, skin eruption and pimples.

Table 8-56 Frequency of Rash Reported as an Adverse Event and Discontinuation due to Rash in Various Populations

Population Treatment Group	Incidence of rash	
	Total n/N (%)	Leading to discontinuation n/N (%)
Therapeutic Studies - Voriconazole	278/1493 (18.6)	13/1493 (0.9)
Overall Pooled -- Voriconazole	362/2090 (17.3)	17/2090 (0.8)
Esophageal Candidiasis Study (305)		
Voriconazole	11/200 (5.5)	2/200 (1.0)
Fluconazole	10/191 (5.2)	0
Empirical Treatment Study (603)		
Voriconazole	96/421 (22.8)	2/421 (0.5)
Liposomal amphotericin B	105/428 (24.5)	3/428 (0.7)
Comparative Aspergillosis Study (307/602)		
Voriconazole	45/196 (23.0)	2/196 (1.0)
Amphotericin B/Other Licensed Antifungal Therapy	40/185 (21.6)	1/185 (0.5)

Two patients were reported with Stevens-Johnson syndrome, one patient (304-0137-0816) was reported with erythema multiforme and one patient (604-1034-6186) had an event described as toxic epidermal necrolysis. Of these, the patients of erythema multiforme and toxic epidermal necrolysis were considered serious and a relationship to voriconazole treatment could not be ruled out.

The case histories for the 4 patients with reported Stevens-Johnson, erythema-multiforme, or toxic epidermal necrolysis are summarized below.

- Patient 604/6201 was a 44 year old male, with a history of actinic keratosis, eczema and acne vulgaris, who was treated with voriconazole for cryptococcosis for 89 days. Probable Stevens-Johnson syndrome (generalized erythema and desquamation) was reported as a serious adverse event on Day 78. There was no histological confirmation of the diagnosis reported. The patient's condition worsened and the investigator attributed the event to concomitant antiretroviral therapy. Voriconazole was not withdrawn. Concomitant antiretroviral therapy was therefore discontinued and the condition improved although it was still present at last patient visit (Day 89).
- Patient 603/1638 was a 47 year old female, with a history of erythema of the hands, who was treated with voriconazole for empirical treatment of persistent fever and neutropenia for 21 days. Stevens-Johnson syndrome was reported as a severe adverse event on Day 3 and the investigator attributed the event to concomitant chemotherapy. There was no histological confirmation of the diagnosis reported. The patient also experienced exfoliative dermatitis (areas of skin denudation on right femur and exfoliation of the epidermis of the right hand) from Day 2 to 17, which was also attributed to chemotherapy by the investigator. Voriconazole was not withdrawn and all the aforementioned events resolved on Day 17.
- Patient 304/0816 was a 28 year old male who was treated with voriconazole for pulmonary aspergillosis for a total of 95 days. The patient developed moderate erythema on the face and arms on Day 87. Voriconazole was temporarily discontinued on Days 89 to 94 while the patient received conditioning and immunosuppression followed by a bone marrow transplant. The erythema worsened on Days 89 to 94 while the patient was receiving carmustine. On Day 97, the third day after voriconazole treatment was restarted, the erythema was exacerbated. Voriconazole was permanently discontinued on Day 102 and the investigator assessed the patient as having a prolonged hospitalization due to erythema multiforme. The investigator attributed the event to the combination of carmustine and voriconazole. The event was reported resolved by Day 147. The Sponsor could not rule out a contribution by voriconazole.
- Patient 604/6186 was a 35 year old male who was treated with voriconazole for *Aureobasidium pullulans* infection for 133 days. On Day 41, the patient developed severe photosensitivity rash which the investigator attributed to voriconazole, and treatment was temporarily discontinued on Day 60. The rash subsided and treatment was restarted on Day 68. On Day 141 rash with blisters on hands, shins and knees 'like toxic epidermal necrolysis' was reported by the investigator as a treatment related serious adverse event and voriconazole was permanently discontinued. The event was reported resolved by Day 154. The Sponsor could not rule out a contribution by voriconazole.

Some of the skin reactions appeared to have an element of photosensitivity. In the Overall Pooled population, 41 (2.0%) of 2090 patients receiving voriconazole reported events that coded to the preferred term of photosensitivity reaction. Photosensitivity reactions are not normally associated with azoles, although one case report of a photosensitivity reaction with voriconazole has been published (Swift and Denning, 1998). Of the 41 events reported in patients treated with voriconazole, only two resulted in discontinuation. Photosensitivity is frequently observed with agents that are likely to be co-administered with voriconazole, such as quinolones or trimethoprim-sulfmethoxazole and are associated with exposure to UV A radiation (320-400nm). Neither voriconazole nor its principal metabolite, UK-121,265, has significant absorption in this region of the spectrum. Outpatients in the voriconazole clinical program were not warned to avoid sunlight during therapy, and the frequency of photosensitivity reaction is still low.

Overall, voriconazole is associated with skin reactions. In addition, a causal association between voriconazole and photosensitivity cannot be ruled out. In view of these results, the voriconazole proposed package insert states that if a photosensitivity reaction is observed, it is recommended that patients avoid sunlight.

8.8.4 Cardiac Function

In the clinical development program, there was a single sudden death, presumed due to cardiac arrhythmia, where a possible relationship to voriconazole could not be excluded. The narrative summary of this patient is:

- Patient 603/1485 died of ventricular fibrillation and voriconazole could not be excluded as a contributing factor, although there were multiple potential precipitating etiologies. The patient was a 52 year old female with acute myeloid leukemia who had a cardiac arrest within 30 minutes of her first infusion of voriconazole of 540 mg. Her medical history recorded sinus bradycardia with ventricular and supraventricular extrasystoles nine years earlier at which time therapy with quinidine and digoxin was initiated. She had completed her first cycle of chemotherapy (including idarubicin) five days before receiving voriconazole. At the time of study she was neutropenic and had received numerous platelet and red blood cell transfusions. She was hypokalemic (3.1mmol/L), hypocalcemic (2.05mmol/L) had severe untreated hypophosphatemia (0.49mmol/L; normal. range-1.13-1.60) and had a magnesium at the lower end of the normal range (0.74 mmol/L, normal range 0.75-1.0 mmol/L). On the day of the event, the patient received potassium chloride as an infusion of 20mEq/L at a rate of 120 ml/hour, and a bolus of 30 mEq in 250 cc 5% dextrose solution. After administration of the bolus for approximately one hour, the infusion was interrupted, the patient was randomized, and received an intravenous dose of voriconazole 540 mg, administered over a two hour period. The cardiac arrest occurred approximately 30 minutes after the completion of the voriconazole infusion. At the time of death she was receiving several medications that could themselves precipitate arrhythmias, including thyroxine, prochlorperazine, diphenhydramine, imipenem, metronidazole and ciprofloxacin. Autopsy showed pronounced left ventricular dilation. This patient had serious underlying cardiac dysfunction which may have been a consequence of previous idarubicin therapy.

As a result of this event, cardiac events and the potential for voriconazole to prolong QT interval have been examined in more detail. In order to include all events that relate to QT prolongation and its possible sequelae, a broad range of treatment emergent adverse events were examined. The comparison of all causality adverse cardiac events reported during study treatment showed a similar in patients receiving voriconazole than those receiving fluconazole in the Esophageal Candidiasis Study (305). Results for the Global Comparative Aspergillosis Study (307/602) and the Empirical Therapy Study (603/MSG42) are shown in Table 8-57.

Table 8-57 Global Comparative Aspergillosis Study (307/602) and Empirical Therapy Study (603/MSG42) - Cardiac Adverse Events

Adverse Event	Global Comparative Aspergillosis Study (307/602)		Empirical Therapy Study (603/MSG42)	
	Voriconazole N=196 n (%)	Amphotericin B/ OLAT N=185 n (%)	Voriconazole N=421 n (%)	Liposomal Amphotericin B N=428 n (%)
Tachycardia	21 (10.7)	26 (14.1)	62 (14.7)	86 (20.1)
Bradycardia	0	1 (0.5)	17 (4.0)	10 (2.3)
Dizziness	9 (4.6)	11 (5.9)	36 (8.6)	24 (5.6)
Arrhythmia				
Atrial*	5 (2.6)	8 (4.3)	12 (2.9)	7 (1.6)
Ventricular**	2 (1.0)	1 (0.5)	7 (1.7)	7 (1.6)
Other#	2 (1.0)	3 (1.6)	7 (1.7)	6 (1.4)
Cardiac Arrest	6 (3.1)	2 (1.1)	5 (1.2)	5 (1.2)
Syncope	5 (2.6)	1 (0.5)	3 (0.7)	1 (0.2)
Electrocardiogram abnormal	1 (0.5)	0	4 (1.0)	3 (0.7)
Atrioventricular block	0	1 (0.5)	0	1 (0.2)
Palpitation	0	1 (0.5)	4 (1.0)	2 (0.5)
Increased QTc	0	0	1 (0.2)	0

* Atrial arrhythmia includes atrial arrhythmia, supraventricular tachycardia and atrial fibrillation;
**Ventricular arrhythmia includes ventricular arrhythmia, ventricular tachycardia and ventricular fibrillation;
Other arrhythmia includes arrhythmia and extrasystoles;

In the Global Comparative Aspergillosis Study (307/602), there were more events of cardiac arrest and syncope in the voriconazole group than the amphotericin B + other licensed antifungal therapy group. While the contribution of voriconazole could not be excluded in every case, clinical review of these cardiac adverse events revealed no obvious pattern within the voriconazole group. One patient receiving voriconazole in the Empirical Therapy Study (603/MSG42) had an increase in QTc considered by the investigator to be related to loading with amiodarone for ongoing atrial fibrillation.

Cardiac adverse events in the pooled safety populations are shown in Table 8-58.

Table 8-58 Pooled Safety Database – Cardiac Adverse Events – Voriconazole Therapeutic Studies and Overall Pooled Populations

Cardiac adverse events	Voriconazole Therapeutic Studies N=1493 n (%)	Voriconazole Overall Pooled Population N=2090 n (%)
Tachycardia	119 (8.0)	134 (6.4)
Bradycardia	31 (2.1)	36 (1.7)
Dizziness	68 (4.6)	79 (3.8)
Arrhythmia		
Atrial*	46 (3.1)	59 (2.8)
Ventricular**	17 (1.1)	24 (1.1)
Other#	16 (1.1)	22 (1.1)
Cardiac Arrest	27 (1.8)	37 (1.8)
Syncope	21 (1.4)	23 (1.1)
Electrocardiogram abnormal	7 (0.5)	7 (0.3)
Atrioventricular block	1 (0.1)	1 (<0.1)
Palpitation	12 (0.8)	13 (0.6)
Increased QTc	1 (0.1)	2 (0.1)

* Atrial arrhythmia includes atrial arrhythmia, supraventricular tachycardia and atrial fibrillation;
**Ventricular arrhythmia includes ventricular arrhythmia, ventricular tachycardia and ventricular fibrillation;
Other arrhythmia includes arrhythmia and extrasystoles;

In addition to this clinical review, nonclinical *in vitro* and *in vivo* data were gathered to examine the potential for voriconazole to cause cardiac arrhythmia. A recently published study has shown that ketoconazole blocks the HERG (human ether-a-go-go related gene) channel *in vitro* and therefore may have the potential to directly prolong QT interval. (Dumaine, *et. al.*, 1998). The sponsor therefore used a similar *in vitro* approach to define the electrophysiological properties of voriconazole, its N-oxide metabolite and ketoconazole (as a positive control). The approach included a combination of three examinations to identify the potential to cause QT prolongation.

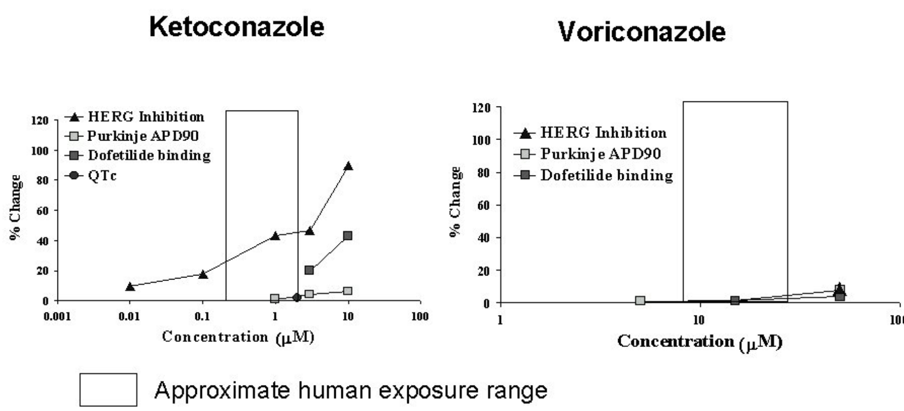
These included:

- effects of voriconazole or ketoconazole on the specific binding of dofetilide to the HERG channel protein
- effects of voriconazole or ketoconazole on HERG current in a patch-clamp assay
- effect of voriconazole or ketoconazole on action potentials recorded from isolated canine Purkinje fibers.

HERG proteins are known to form the channel underlying the cardiac rapidly activating delayed rectifier current I_{Kr}. Agents that block HERG delay repolarization and thereby prolong the cardiac action potential, and are seen on the electrocardiogram as a prolongation of the QT interval. The direct effects of voriconazole on HERG can be assessed using both dofetilide-binding and patch-clamp studies of HERG current. The Purkinje fiber preparation allows the effect on action potential duration to be assessed and this preparation is sensitive to agents known to prolong the electrocardiogram QT interval in animals and human beings. The Purkinje fiber is accepted as the preparation of choice to determine the potential of compounds to prolong the QT interval in human beings. Drugs which do not show substantial effects in these tests at appropriate concentrations are unlikely to lead to clinically relevant effects on QT interval.

Figure 8-2 below shows the results of these three tests for voriconazole and ketoconazole across a wide concentration range.

Figure 8-2 ***In vitro* Studies Performed to Define the Electrophysiological Properties of Voriconazole and Ketoconazole**



Voriconazole did not inhibit activated HERG channels or specific radioligand binding of [^{3}H]-dofetilide to HERG. The highest concentrations of voriconazole and ketoconazole showed an increase on the duration of the action potential at 90% repolarization (APD_{90}) of less than 10%, which is below the limit of detection of this model. The changes were not significantly different from control values and there was no effect on the duration of the action potential (msec) from the upstroke to 50% repolarization (APD_{50}). In contrast, ketoconazole produced full or partial effects on HERG inhibition and dofetilide binding but not on action potential duration. The N-oxide metabolite of voriconazole was tested on [^{3}H]-dofetilide binding and Purkinje fibers and there was no effect seen at a concentration of 50 μM.

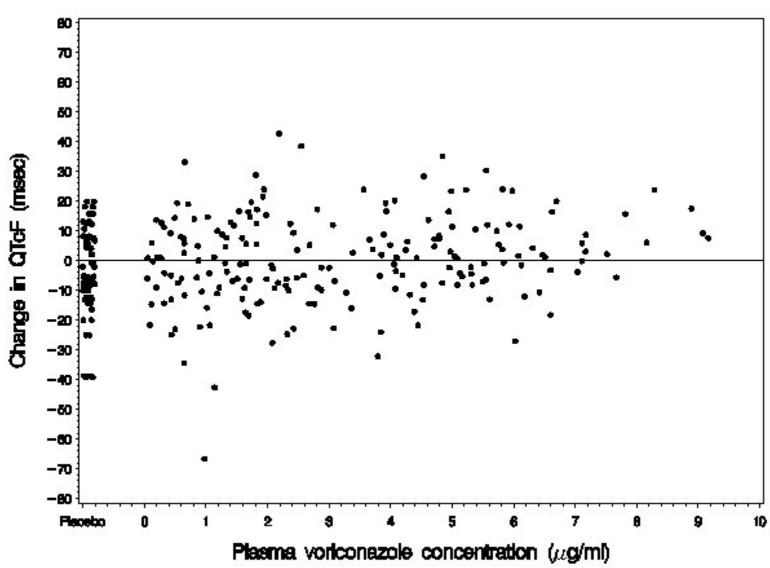
This lack of effect of voriconazole at 50μM, well above the concentrations observed in patients, provides reassurance of the cardiac safety of voriconazole.

In the nonclinical *in vivo* studies, voriconazole administered up to the maximum tolerated dose of 6mg/kg IV had no effects on the electrocardiogram of either conscious or anesthetized dogs. At higher doses, the anesthetized dogs also had inconsistent QT interval changes. One anesthetized animal developed AV nodal premature beats at plasma concentrations well above those observed in the clinical program. The event was not related to dose, continuing unchanged when a higher dose was given and it was not considered a sign of proarrhythmia. QT prolongation was not observed in dogs in the toxicology program where animals were exposed to peak plasma voriconazole concentrations of up to 62.2 μg/ml, a concentration that is approximately three-fold the maximum plasma concentration observed in any patient.

There was no visually apparent relationship between increases in the rate-corrected QT interval (QT_c) and either dose or exposure to voriconazole in the Phase 1 healthy volunteer program. This was true for single doses, for absolute values of QT_c as well as for increases from baseline. This was also the case regardless of whether Bazett's (QT_c=QT/[RR]$^{1/2}$) or Fridericia's formula (QT_c=QT/[RR]$^{1/3}$) was used to correct for heart rate.

Plasma concentrations up to 9.2 μg/ml were measured in the Phase 1 studies. In the Therapeutic Studies Safety population, 90% of patients had maximum plasma voriconazole concentrations less than 9 μg/ml. Central reading of electrocardiograms collected during the Phase 1 studies was performed and were correlated with plasma concentrations at one hour post-single dose in 119 subjects (116 voriconazole-treated subjects and 35 placebo-treated subjects) from the clinical pharmacology studies population. These provide reassurance that, in healthy human subjects in a controlled setting, voriconazole does not produce any important effect on QT interval corrected for heart rate. Figure 8-3 shows the change in QTcF (Fredericia's correction formula) from baseline *vs.* placebo and plasma voriconazole concentration one hour after single dose.

Figure 8-3 Change in QTc (Fredericia's Correction Formula) from Baseline *vs.* Voriconazole Concentration – Clinical Pharmacology Studies



In conclusion, review of the clinical data indicates that voriconazole does not have a noteworthy adverse cardiac profile. Analysis of healthy volunteer QT interval data at plasma concentrations likely to be observed in the majority of patients does not indicate an effect on QTc. The *in vitro* data indicate that voriconazole showed no inhibition of activated HERG channels or specific inhibition of radioligand binding of [^{3}H]-dofetilide to HERG.

8.8.5 Sepsis and Host Resistance

Vora *et al.* (1998) showed that when added to neutrophils, voriconazole produced an additive effect with regard to inhibition of *Aspergillus* spp. hyphae as well killing of *C. albicans* and was more potent than fluconazole in augmenting antifungal activity of neutrophils or monocytes. In a Sponsor-conducted study, proliferation of basal and mitogen-stimulated lymphocytes was unaffected by both voriconazole and fluconazole at a concentration of 25µM, but was significantly inhibited by ketoconazole and itraconazole at concentrations ranging from 5 to 25µM. In rat and dog toxicology studies, there were few voriconazole effects on hematological parameters; only minor changes in leukocyte counts were reported in chronically dosed rat studies.

The time to neutrophil recovery in the Empirical Therapy Study (603) was examined in detail. The median time to recovery from neutropenia (considered to be more than 250 neutrophils/mm^3) was 5.46 days for the voriconazole arm and 5.52 days for the liposomal amphotericin B arm. The hazard ratio of voriconazole to liposomal amphotericin B is 1.01 with a p value of 0.84 and an approximate two-sided 95% confidence interval of 0.88 to 1.17, confirming that there is no evidence of a statistically significant difference between the groups. The probability of recovery of neutrophils 14 days after randomization was 0.86 for voriconazole and 0.85 for liposomal amphotericin B. A similar number of patients in both treatment groups recovered from neutropenia during treatment or at follow-up, 347/415 on voriconazole (83.6%) and 376/422 on liposomal amphotericin B (89.1%). These analyses suggest that there is no evidence of a myelosuppressive effect associated with voriconazole therapy.

To examine sepsis, patients were initially identified from the project database adverse event listings. A broad search of preferred terms, investigator text and causality for the adverse event terms of “sepsis”, “septic shock”, “septicemia”, “bacteremia”, “line sepsis”, and “catheter/line infection”, defined as “broad sepsis”. Review of the frequency of project sepsis and broad sepsis in these three comparative, open-label studies, demonstrates more spontaneously reported sepsis events in the voriconazole-treated patients.

As part of the investigation, the Sponsor also examined the patients with sepsis and identified those who had documented bacterial infection. As microbiology was prospectively collected in all patients in the Empirical Therapy Study (603), results from this study were examined most closely. Among patients with broad sepsis in the Empirical Therapy Study (603), 44/421 voriconazole patients (10%) and 38/428 liposomal amphotericin B patients (9%) had documented bacterial infections. This difference is not statistically significant, nor was the difference in time to onset of bacterial infection by Kaplan-Meier time to event analysis.

The data available from both nonclinical and clinical investigations do not support a causal relationship between voriconazole therapy and either decreased host defense or sepsis.

8.8.6 Renal Function

A review of the literature does not suggest that azole antifungal agents are causally associated with renal toxicity, although adverse events related to renal function are frequently observed in the patient populations at greatest risk of fungal infection. The patients studied within the voriconazole clinical trial program were largely immunocompromised with severe underlying conditions ranging from advanced AIDS to hematological malignancy. They were susceptible to developing acute renal failure as a result of pre-renal causes (such as fluid imbalance due to diarrhea, vomiting or use of diuretics, heart failure, fever and sepsis) and post-renal causes (such as tubular necrosis) as a result of concomitant nephrotoxic medication use (Thadhani *et al*., 1996). Acute renal failure is well established as a major complication of bone marrow transplantation (Gruss *et al*., 1995; Pulla *et al*., 1998).

Appendix 9 presents literature information on the frequency of renal adverse events in subjects with neutropenia and bone marrow transplantation.

Review of the renal adverse events occurring in voriconazole-treated patients shows a frequency similar to that reported in the literature with other antifungal drugs. Data from two large comparative Phase 3 trials allows direct comparison of voriconazole to amphotericin B + Other Licensed Antifungal Therapy (in the Global Comparative Aspergillosis Study [307/602]) and to liposomal amphotericin (in the Empirical Therapy Study [603]).

Table 8-59 presents the occurrences of renal adverse events and clinically significant renal function test abnormalities in the Empirical Therapy Study (603) and the Global Comparative Aspergillosis Study (307/602).

Table 8-59 Global Comparative Aspergillosis Study (307/602) and Empirical Study (603) - Renal Adverse Events and Clinically Significant Renal Function Tests – Safety (Study 307/602) and Safety (Study 603) Populations

	Empirical Therapy Study (603)		**Global Comparative Aspergillosis Study (307/602)**	
	Voriconazole (N = 421)	**Liposomal amphotericin B (N = 428)**	**Voriconazole (N = 196)**	**Amphotericin B/OLAT* (N = 185)**
Renal adverse event n (%)				
Acute renal failure	25 (5.9)	18 (4.2)	7 (3.6)	17 (9.2)
Renal function abnormal	21 (5.0)	34 (7.9)	18 (9.2)	43 (23.2)
Creatinine elevated	16 (3.8)	36 (8.4)	10 (5.1)	64 (34.6)
Hypokalemia	60 (14.3)	106 (24.8)	18 (9.2)	47 (25.4)
Clinically significant renal function test abnormalities – irrespective of baseline n/N (%)				
Creatinine (> 1.3 X ULN)	54/410 (13.2)	66/411 (16.1)	39/182 (21.4)	102/177 (57.6)
Blood urea nitrogen (> 1.3 X ULN)	96/401 (23.9)	113/402 (28.1)	25/63 (39.7)	49/62 (79.0)
Potassium (< 0.9 X ULN)	101/413 (24.5)	165/413 (40.0)	30/181 (16.6)	70/178 (39.3)

OLAT = Other Licensed Antifungal Therapy; ULN = upper limit of normal

Literature reports of the use of azole antifungal agents in non-cancer patients do not generally contain high rates of renal adverse events (Graybill *et al*., 1990; de Beule *et al*., 1991; Inman *et al*., 1993; Haubrich *et al*., 1994). Review of the renal adverse events occurring in voriconazole-treated non-cancer patients shows a similar low frequency. Data from a large comparative Phase 3 trial allows direct comparison of voriconazole to fluconazole (in the Esophageal Candidiasis Study [305]). Table 8-60 presents the occurrences of renal adverse events and clinically significant renal function test abnormalities in this study.

Table 8-60 Esophageal Candidiasis Study (305) - Renal Adverse Events and Clinically Significant Renal Function Test Abnormalities – Intention to Treat Population

Renal Adverse Event	Voriconazole (N = 200)	Fluconazole (N = 191)
Renal adverse event n (%)		
Acute renal failure	0	0
Renal function abnormal	2 (1.0)	1 (0.5)
Creatinine elevated	1 (0.5)	1 (0.5)
Hypokalemia	1 (0.5)	2 (1.0)
Clinically significant renal function test abnormalities – irrespective of baseline n/N (%)		
Serum creatinine (> 1.3 X ULN)	7/187 (3.7)	7/186 (3.8)
Urea (>1.3 X ULN)	7/174 (4.0)	7/174 (4.0)
Potassium (<0.9 X ULN)	6/187 (3.2)	12/186 (6.5)

The occurrence of renal adverse events and clinically significant renal function test abnormalities was similar in the voriconazole-treated and the fluconazole-treated patients.

Voriconazole did not affect renal function in nonclinical general pharmacology studies. Voriconazole was investigated for its effects on urinary pH and the excretion of urine and electrolytes, over a five hour period after dosing, by normotensive female rats given an oral saline load. At doses of 1, 3 and 10mg/kg PO, voriconazole did not affect urine volume or pH or the excretion of sodium, potassium or chloride, indicating no apparent effect on renal function. In toxicology studies, oral voriconazole did not affect renal function.

The vehicle used with intravenous voriconazole, sulfobutylether-β-cyclodextrin (SBECD), did produce histological alterations in the epithelium of the proximal renal tubule of rats and dogs; the alterations were vacuoles. The histological changes did not progress to degenerative changes in animals administered intravenous SBECD for up to six months and renal function, in terms of serum creatinine and urea levels remained normal. Creatinine increases were only seen at an extremely high intravenous dose (3g/kg/d) in a 30-day rat toxicology study. This dose represents a 15-fold multiple of the maximum human dose of SBECD, given in the Day 1 loading dose of voriconazole (200mg/kg SBECD).

The potential effects of SBECD on renal function and integrity were measured in two clinical trials in which SBECD was given twice daily to healthy volunteers, the Radiolabelled SBECD Study (227, 10 day administration) and the Intravenous Oral Maintenance Dose Setting Study (230, seven day administration) at doses up to 320mg/kg/d. Sensitive urinary markers of renal integrity or function (including N-acetylglucoseaminidase [NAG], β-2-microglobulin and creatinine) were measured, in addition to standard blood chemistry measurements of urea and creatinine. From these data, there was no evidence to suggest SBECD as a cause of renal dysfunction.

SBECD is exclusively excreted by the kidney and accumulates in patients with impaired renal function. The consequence of accumulation is not known, however it is possible that in patients with impaired renal function, SBECD plasma concentrations will approach those in the 30-day rat study, during which elevations in serum creatinine were seen. In a clinical study of intravenous voriconazole in patients with impaired renal function, two of six patients with moderate renal impairment and baseline serum creatinine >2.5mg/dL had elevations of serum creatinine during treatment with voriconazole. Creatinine resolved to baseline in both volunteers after discontinuation of therapy (one of whom had already completed the 7-day treatment period, before the creatinine elevation was seen). Accordingly, because SBECD is excreted exclusively by the kidney, clinical trial protocols recommended oral therapy if a patient's serum creatinine concentration was 2.5mg/dL.

Overall, although there is little evidence to indicate a nephrotoxic potential with voriconazole use, it is recommended that serum creatinine be monitored following administration of voriconazole.

8.8.7 Hallucinations

In the Overall Pooled population, hallucinations were reported by 98 of 2090 voriconazole-treated patients (4.7%) and 22 of 856 active control-treated patients (2.6%). Active control-treated patients reporting hallucinations were receiving either fluconazole, conventional amphotericin B or liposomal amphotericin B. The majority of those occurring with voriconazole (56/98, 57%) were observed in the Empirical Therapy Study (603). In this study, hallucinations resulted in discontinuation in seven patients (7/56, 12.5%).

Voriconazole-treated patients who experienced hallucinations had a number of confounding factors, including underlying fever and the concomitant use of opiates, benzodiazepines and other central nervous system active medications. In addition, some reports of hallucinations may be related to visual disturbances. Despite these confounding factors, a contribution of voriconazole cannot be excluded.

8.9 Conclusions

Safety assessment in over 2000 patients demonstrates that voriconazole is associated with visual abnormalities, hepatic function abnormalities, and skin reactions. Visual abnormalities are transient and reversible. An extensive nonclinical and clinical evaluation suggests that the retina is the target site of activity but there is no evidence to suggest long term sequelae. Liver function test monitoring during voriconazole treatment is recommended; the target population is at risk of hepatic damage because of underlying illness and concomitant medication use, as well as potential effects of voriconazole. Voriconazole is associated with skin reactions and may be associated with photosensitivity; patients who experience photosensitivity should avoid sunlight exposure.

Voriconazole was demonstrated to be better tolerated than amphotericin B formulations. Patients were maintained on therapy for longer durations and voriconazole was associated with fewer infusion related reactions, hypokalemia, and increases in serum creatinine. In a comparison with fluconazole in a primarily HIV positive population of patients with esophageal candidiasis, the safety profile of voriconazole was acceptable; however, more patients discontinued therapy with voriconazole and there were more liver function test abnormalities with voriconazole.

9 DOSE JUSTIFICATION

9.1 Dose Confirmation

Following the completion of therapeutic studies, exploratory pharmacokinetic/pharmacodynamic analyses were conducted to assess the appropriateness of the dose regimens used. Plasma voriconazole concentrations observed in therapeutic studies were compared with MICs from clinical isolates. Given the wide inter-individual variability in voriconazole pharmacokinetics, analyses were also conducted to assess whether the risk/benefit could be optimized by plasma concentration monitoring.

The relationships between plasma voriconazole concentrations and both efficacy and safety endpoints were explored. Liver function test results were used as the relevant safety endpoints. Depending on the study, the efficacy endpoint was an expert, Data Review Committee or a sponsor-assessed response at end of treatment (Table 9-1). The pharmacokinetic/pharmacodynamic analyses included graphical and tabular presentations as well as multiple linear and logistic regression and survival analysis (for time-to-event data).

Table 9-1 Summary of Efficacy Assessments in Therapeutic Studies Used in the Pharmacokinetic/Pharmacodynamic Analyses

Study	Assessment of Efficacy
303	Sponsor
304	External Expert
305	Sponsor
309	Sponsor
603	External DRC
604	Sponsor
608	External DRC

In 10 therapeutic studies, blood samples for the measurement of plasma voriconazole concentrations were collected from patients at various time points during treatment. More than one blood sample could be collected during a specific dose interval or on different days of treatment. The median number of plasma concentration measurements per patient was 3 (range = 1 - 21). More than 75% of patients had plasma voriconazole concentration measurements. There were 3736 plasma voriconazole concentration measurements from 1053 patients at the time of NDA submission. In these 1053 patients, the median of average and maximum plasma concentrations in individual patients across the studies were 2.51 µg/ml (inter-quartile range = 1.16 – 4.45 µg/ml) and 3.77 µg/ml (inter-quartile range = 2.03 – 6.31 µg/ml), respectively.

In the Global Comparative Aspergillosis Study (307/602), 618 plasma voriconazole concentration measurements were made in 155 of the 196 voriconazole-treated patients (79%). The median number of samples per patient was 4, with a range of one to 10. In these 155 patients, the median of average and maximum plasma concentrations in individual patients were 2.66 µg/ml (inter-quartile range = 1.60 – 4.18 µg/ml) and 4.44 µg/ml (inter-quartile range = 2.75 – 7.11 µg/ml), respectively. Of the 144 patients included in the Modified Intention to Treat population, 116 (81%) had plasma voriconazole concentration measurements.

Table 9-2 NDA Therapeutic Studies and Global Comparative Aspergillosis Study (307/602) - Use of Plasma Voriconazole Concentration Data in Various Pharmacokinetic/Pharmacodynamic Analyses and Presentations

Dataset	N	Pharmacokinetic/Pharmacodynamic Analysis/Presentation
NDA Therapeutic Studies	1214	
Total with plasma concentrations	1053	PK/PD and predictive value analysis for LFT abnormalities
Total with plasma concentrations and efficacy data from VERA	453	Predictive value analyses for Candidiasis and Aspergillosis
Total with plasma concentrations and efficacy data from VERA (excluding Study 305)	280	PK/PD for efficacy
Global Comparative Aspergillosis Study (307/602) MITT efficacy population with plasma concentrations	116	PK/PD for efficacy

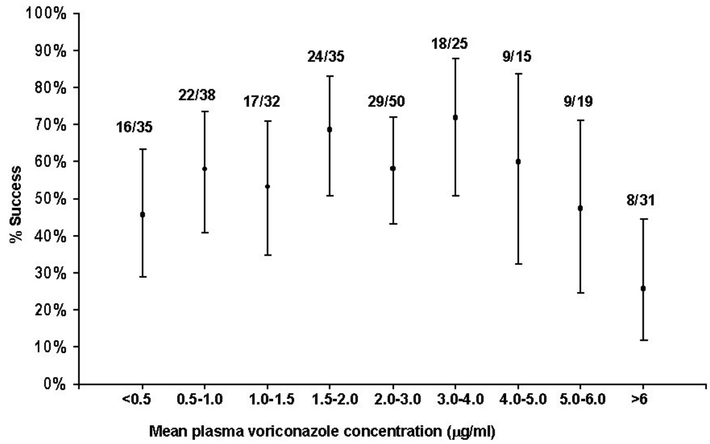
MITT = Modified Intention to Treat; LFT = liver function tests; PK/PD = pharmacokinetic/pharmacodynamic; VERA = Voriconazole Efficacy Response Assessment

9.1.1 Pharmacokinetic/Pharmacodynamic Relationship Between Plasma Voriconazole Concentration and Efficacy

For pharmacokinetic/pharmacodynamic analyses of efficacy, mean plasma voriconazole concentration from start to end of therapy was calculated for each patient. A combined pharmacokinetic/pharmacodynamic analysis of all infections was conducted on data from Studies 303, 304, 309, 603, 604 and 608 (n=280) from the NDA Clinical Pharmacology Studies. This efficacy analysis was conducted omitting Study 305 because esophageal, rather than systemic, fungal infection was being treated and the study had an overall high success rate (98.3% in voriconazole-treated patients in the primary efficacy analysis). The pharmacokinetic/pharmacodynamic relationship for efficacy in the Global Comparative Aspergillosis Study (307/602) was explored separately.

The relationship between mean plasma voriconazole concentrations and efficacy in all infections is presented in Figure 9-1.

Figure 9-1 Relationship Between Plasma Voriconazole Concentrations and Efficacy



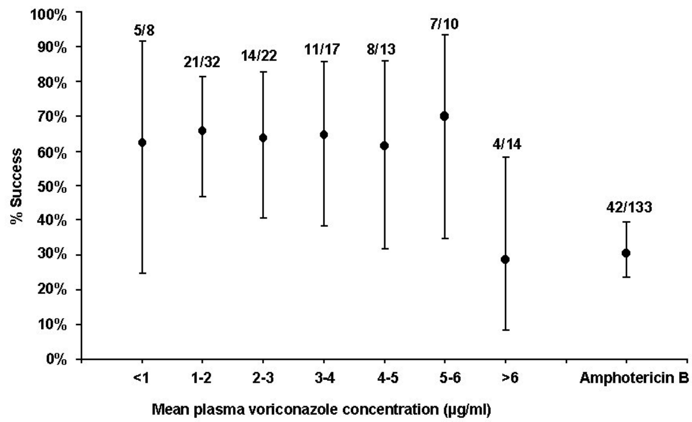
*Proportion of patients with successful outcomes and 95% confidence intervals are shown (data from Studies 303, 304, 309, 603, 604, and 608, n=280) from the NDA Clinical Pharmacology Studies

The proportion of treatment successes in patients with mean plasma voriconazole concentration below 0.5 μg/ml was slightly lower than in those patients with mean plasma voriconazole concentration between 0.5 and 5.0 μg/ml but the difference did not achieve statistical significance.

Reduced efficacy was observed in patients with the highest plasma voriconazole concentrations. Review of the patients with the higher plasma voriconazole concentrations (> 6 μg/ml) provided evidence that the patients had hepatic impairment and severe underlying medical conditions that influenced clinical outcome. Therefore the pharmacokinetic/pharmacodynamic relationship between plasma voriconazole exposure and clinical outcome was significantly confounded by complicating medical factors.

A similar finding was observed for the pharmacokinetic/pharmacodynamic relationship in the Global Comparative Aspergillosis Study (307/602), (Figure 9-2).

Figure 9-2 Global Comparative Aspergillosis Study (307/602) - Relationship Between Plasma Voriconazole Concentrations and Efficacy*



* Proportion of patients with successful outcomes and 95% confidence interval are shown (n = 116 for voriconazole patients with plasma samples)

9.1.2 Pharmacokinetic/Pharmacodynamic Relationship Between Plasma Voriconazole Concentration and Liver Function Test Abnormalities

For pharmacokinetic/pharmacodynamic analyses of longitudinal presentation of hepatic enzyme data, the raw pharmacokinetic data were summarized as seven-day mean plasma concentrations, with one plasma concentration per weekly window. This allowed the greatest number of liver function tests measurements to be associated with plasma voriconazole concentrations and is likely to provide the highest sensitivity for the detection of pharmacokinetic/pharmacodynamic relationships. While pharmacokinetic samples may have been taken over any part of the dose interval, intraindividual variability in plasma voriconazole concentrations within the dose interval and between doses is low compared with interindividual variability (see Sec. 6.10). Therefore the mean plasma voriconazole concentrations are adequate for the characterization of differences in exposure between individuals.

The definition of liver function test abnormalities in therapeutic studies accounted for potential abnormalities at baseline. Maximum values within each weekly window were used. Test result abnormalities were investigated for each test individually. Abnormality criteria for liver function tests are summarized in Table 9-3.

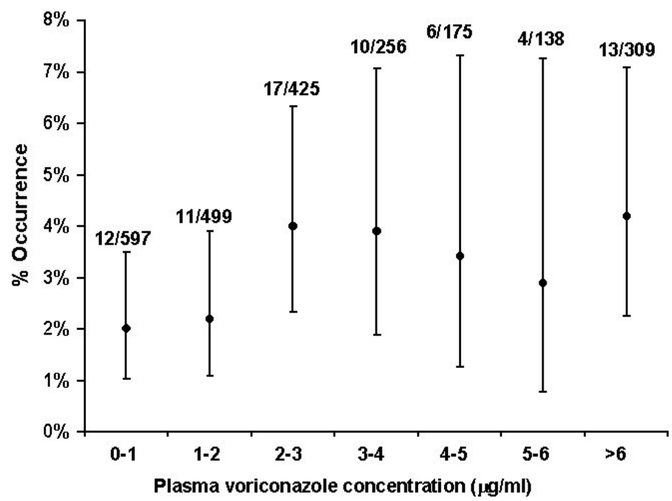
Table 9-3 Abnormality Criteria for Liver Function Tests

Test	Baseline	Result
ALT, AST and alkaline phosphatase	<2 x ULN	≥ 5 x baseline
	≥ 2 x ULN and < 5 x ULN	≥ 3 x baseline
	≥ 5 x ULN and < 10 x ULN	≥ 2 x baseline
	≥ 10 x ULN	≥ 1.5 x baseline
Total bilirubin		≥ 3mg/dl and > baseline

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal

Over the summarized plasma concentration bands of 1 µg/ml (0-1, 1-2, 2-3 µg/ml *etc.*), the weekly occurrence of abnormalities was low with maximum rates of approximately 8%, 10%, 5% and 14% for ALT, AST, alkaline phosphatase and total bilirubin abnormalities, respectively. The relationship between plasma voriconazole concentration and weekly occurrences of ALT abnormalities is presented in Figure 9-3.

Figure 9-3 Relationship Between Plasma Voriconazole Concentration and Weekly Occurrences of Alanine Transaminase (ALT) Abnormalities – Therapeutic Studies*



* Weekly occurrence of ALT abnormalities and 95% confidence intervals are shown against the corresponding weekly mean plasma voriconazole concentrations

Longitudinal logistic regression showed that liver function test abnormalities (AST, alkaline phosphatase and total bilirubin) were statistically significantly but weakly associated with plasma voriconazole concentration, after adjusting for covariates. Similarly, survival analysis (Cox regression) showed that time to first liver function test abnormalities (ALT, AST, alkaline phosphatase and total bilirubin) was associated with plasma voriconazole concentration. The 95% confidence intervals indicated that the increase in the odds or hazard of a liver function test abnormality may be as small as 0% or as large as 27% per 1.00 µg/ml increase in plasma voriconazole concentration. To investigate potential threshold effects, the continuous plasma concentration term was replaced by a series of binary categorical variables defined by plasma concentration above and below various threshold values (1, 2, 3 µg/ml, etc.). These investigations did not identify threshold plasma concentrations above which the risk of a liver function test abnormality was higher compared with plasma concentrations below the threshold.

9.1.3 Plasma Voriconazole Concentrations, MIC and Clinical Outcome

Over 95% of all clinical fungal isolates tested had MICs at or below 1.0 µg/ml. In therapeutic studies, 86.8% (914/1053) of patients with plasma samples attained a plasma voriconazole concentration over 1.0 µg/ml. In the Global Comparative Aspergillosis Study (307/602), 81.01% (94/116) of patients with plasma samples had all plasma voriconazole concentrations greater than the MIC_{90} (0.5 µg/ml) for *Aspergillus* spp. These data from therapeutic studies confirmed that the dose regimens used achieved the desired plasma voriconazole concentrations relative to the MICs in clinical isolates. Investigations of the relationship between MIC or mean plasma concentration/MIC ratio and clinical outcome, did not reveal any obvious relationships. A Cured or Improved clinical outcome was recorded for 7 of 11 patients with *Candida* isolates for which the isolates' voriconazole MICs exceeded the *Candida* species MIC_{90}. The MICs of some of these isolates even exceeded the mean plasma voriconazole concentration (notably in some patients with *C. tropicalis* infection) and yet these patients had successful outcomes. This was also be observed for other fungi, most notably the *Fusarium* isolates. Consistent with the complex clinical picture of many of the patients treated in the voriconazole program, a clear relationship between MIC and clinical response outcome remains to be established.

9.1.4 Analyses of the Potential Predictive Value of Plasma Voriconazole Concentrations

The predictive value of plasma voriconazole concentrations collected during the therapeutic studies was assessed for both efficacy and liver function test abnormalities. Details of this analysis, which was not included in the November 2000 New Drug Application, are found in Appendix 9. This analysis did not identify upper and lower threshold plasma concentrations which are predictive of liver function test abnormalities and therapeutic failure, respectively.

9.2 Voriconazole Dosing Regimen

The recommended voriconazole dosing regimen starts with two loading doses 12 hours apart, followed by a q 12 h maintenance dose regimen (Table 9-4).

Table 9-4 Voriconazole Dosage and Administration

	INTRAVENOUS	ORAL	
		Patients 40kg and above	**Patients less than 40kg**
Loading Dose Regimen (first 24 hours)	Two doses of 6 mg/kg 12 hours apart	Two doses of 400mg 12 hours apart	Two doses of 200mg 12 hours apart
Maintenance Dose (after first 24 hours):			
Serious *Candida* infections Empirical Therapy	3 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours
Invasive aspergillosis / *Scedosporium* and *Fusarium* infections / other serious mould infections	4 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours

The 3mg/kg IV q 12 h maintenance dose was used in the majority of patients in the clinical program. The intravenous dose should be infused at a maximum rate of 3 mg/kg/hour.

The higher maintenance dose of 4 mg/kg IV in aspergillosis and other mould infections is supported by the safety and efficacy results of the randomized open label Global Comparative Aspergillosis Study (307/602). An initial oral maintenance dose of 200 mg q 12 h is recommended rather than 300 mg q 12 h from considerations of hepatic safety from Multiple Dose Escalation IV/Oral Switch Study (230).

The severe underlying conditions of patients who are to receive voriconazole may result in under- or malnourishment and, as a consequence, they may have lower than normal body weights. Since dosing advice for intravenous use of voriconazole is based on body weight, no adjustment is needed for lighter individuals, however oral use of voriconazole is based on a fixed dose, where excessive plasma concentrations may occur if a standard 200mg dose is given. A 200 mg dose is equivalent to 5 mg/kg in a 40 kg patient. Since this dose was associated with liver function test elevations in Multiple Dose Escalation IV/Oral Switch Study (230), it is advised that the oral dose regimen for patients under 40 kg be half the standard dose (*i.e.* 100 mg q 12 h).

With consideration of the non-linear pharmacokinetics of voriconazole, provision is made for dose increase if there is a poor response, and for dose reduction (from the higher maintenance dose) if tolerability issues arise. The adverse drug reaction requiring monitoring and management most frequently at high concentrations is a rise in liver function tests.

If patient response is inadequate, the maintenance dose of 3 mg/kg every 12 hours may be increased to 4 mg/kg every 12 hours for intravenous administration and to 300 mg every 12 hours for oral dosing. For patients less than 40 kg, the oral dose may be increased to 150 mg every 12 hours.

9.3 Conclusions

Doses of voriconazole were chosen for investigation in therapeutic studies on the basis of mycological, pharmacokinetic and clinical data. The intravenous dose regimen of 6mg/kg 12 hours apart for two doses followed by maintenance doses of 3 mg/kg q 12 h rapidly achieved steady state plasma concentrations higher than the MICs for the majority of clinically relevant fungal pathogens. The Dose Ranging Oropharyngeal Candidiasis Study (302) defined the lower end of the dose-response relationship for the treatment of candidiasis. The Multiple Dose Escalation IV/Oral Switch Study (Study 230) showed that the risk of liver function test elevations increased with dose, and supported administration of a maintenance dose of 3mg/kg IV q 12 h or 200mg orally q 12 h, with the option of dose escalation in the face of poor clinical response. Because of the serious nature of the infection, an intravenous maintenance dose regimen of 4 mg/kg q 12 h was used in the Global Comparative Aspergillosis Study (307/602) with a favorable benefit to risk ratio.

The pharmacokinetic/pharmacodynamic analyses demonstrated statistically significant but weak relationships between plasma voriconazole concentration and the occurrence of liver function test abnormalities. The pharmacokinetic/pharmacodynamic relationship for efficacy was confounded by other medical factors. However, successful outcome was achieved across range of plasma voriconazole concentrations observed from the dosage regimens studied. The dose regimen of voriconazole studied is likely to represent the top end of the dose-response curve.

Pharmacokinetic data from therapeutic studies confirmed that the dose regimens used achieved the desired plasma voriconazole concentrations which exceed the MICs for clinical isolates.

Analyses of the potential predictive value of plasma voriconazole concentration monitoring did not identify upper and lower threshold plasma concentrations which are predictive of liver function test abnormalities and therapeutic failure, respectively (see Appendix 8). Dosage individualization on the basis of plasma voriconazole concentration measurements will not add value to monitoring of liver function tests. Interpreting plasma voriconazole concentrations is difficult in the clinical setting which may be complicated by host, pathogen and underlying disease factors.

In summary, analyses of the plasma voriconazole concentrations from therapeutic studies for pharmacokinetic/pharmacokinetic relationships, coverage of MICs and potential predictive performance confirm that the recommended dose regimens of voriconazole are appropriate for the proposed indications.

10 SUMMARY OF BENEFITS AND RISKS

There is a high morbidity and mortality associated with fungal infections, in particular those due to *Aspergillus* spp. (Patterson, *et. al.* 2000). The treating physician has few therapeutic options since available therapies are limited by poor spectrum of antifungal activity, toxicity or the lack of both IV and oral formulations. Voriconazole was developed to address this unmet medical need.

Voriconazole is a second generation triazole and is the result of a development program aimed at improving the potency and spectrum of fluconazole. Thus, voriconazole was designed to retain the parenteral and oral formulation advantages of fluconazole while extending its spectrum to moulds and less common pathogens. The possibility of voriconazole therapy using either IV or oral formulations allows flexibility in patient care and the possibility of prolonged treatment.

Voriconazole has broad *in vitro* antifungal activity against yeasts and moulds, including a wide range of less common pathogens. Voriconazole is fungicidal *in vitro* against all *Aspergillus* spp. and a range of moulds such as *Scedosporium spp.* and *Fusarium spp*., which have limited susceptibility to available antifungal agents. Voriconazole is also highly potent against *Candida* spp. This potent, antifungal activity observed *in vitro* with voriconazole translates to excellent comparative efficacy against aspergillosis and candidiasis *in vivo*, in severely immunocompromised guinea pig models.

The pharmacokinetics of voriconazole are characterized by high oral bioavailability, large volume of distribution, cytochrome P450-mediated hepatic elimination, non-linearity, wide interindividual variability and genetic polymorphism in the CYP2C19 route of metabolism. The high oral bioavailability (96%) of voriconazole allows switching of intravenous and oral treatment and the large volume of distribution (4.6 L/kg) demonstrates extensive distribution to tissues. An extensive clinical program has provided the appropriate pharmacokinetic information to facilitate dose selection, explain the pharmacokinetic variability and provide practical guidance on dosage adjustment in special populations where clinically relevant.

The potential for voriconazole to interact with other medications has been studied in an extensive series of *in vitro* and clinical pharmacology studies. Voriconazole is a substrate of CYP2C19, CYP2C9, and CYP3A4. Potent inducers of cytochrome P450 markedly decrease plasma voriconazole concentrations, however, other inhibitors of cytochrome P450 either have a minor or no effect on voriconazole exposure. Voriconazole inhibits CYP2C19, CYP2C9 and CYP3A4 with potential to increase exposure to a number of concomitant medications metabolized by these isozymes. The magnitude of interactions with CYP3A4 substrates is, however, variable ranging from no interaction (indinavir) to large increases in exposure (sirolimus).

The role of voriconazole in the treatment of fungal infection has been studied in a large clinical program in which its efficacy and safety have been comprehensively evaluated. Voriconazole is anticipated to have greatest utility in subjects who are particularly at risk for systemic fungal infections, including those with bone marrow transplantation, graft vs. host disease and prolonged neutropenia. Voriconazole has been studied for safety and efficacy in patients with aspergillosis, candidiasis, and infections due to emerging pathogens and in the empirical treatment of febrile neutropenia.

In the randomized open label Global Comparative Aspergillosis Study (307/602), voriconazole patients with documented invasive aspergillosis experienced better rates of successful outcome and survival than those receiving amphotericin B followed by Other Licensed Antifungal Therapy. Comparison of the safety data from the voriconazole Initial Randomized Therapy period with the amphotericin B + Other Licensed Antifungal Treatment regimen shows that the safety and tolerability of voriconazole is superior to amphotericin B + Other Licensed Antifungal Therapy. With the exception of visual disturbances, the majority of adverse events were reported at a lower rate in the voriconazole group. Hepatic function laboratory abnormalities occurred at a similar frequency in both treatment arms, and renal function laboratory abnormalities occurred more often in the amphotericin B + Other Licensed Antifungal Therapy group. Overall, the results in the randomized open label Global Comparative Aspergillosis Study (307/602) show a positive benefit for voriconazole treatment in comparison to the risks and support the indication of treatment of aspergillosis.

The success rates seen with voriconazole in the randomized open label Global Comparative Aspergillosis Study (307/602) confirmed the results of the earlier Non-comparative Aspergillosis Study (304); success rates in the amphotericin B arm of the Global Comparative Aspergillosis Study (307/602) were similar to those seen in the Historical Control Study (1003). Success rates due to voriconazole therapy were also similar in the pooled aspergillosis efficacy analysis. The evidence for efficacy includes successful outcomes and survival among patients with central nervous system aspergillosis and efficacy in patients with allogeneic bone marrow transplantation including those with graft *vs.* host disease. The results in the Non-comparative Aspergillosis Study (304) and the pooled analysis provide additional evidence of the benefit of voriconazole treatment of aspergillosis.

In the Esophageal Candidiasis Study (305), voriconazole was not inferior to effective as fluconazole in the treatment of esophageal candidiasis. Although the safety of voriconazole was acceptable in this study, there were more discontinuations due to adverse events and more hepatic function abnormalities in the voriconazole group than the fluconazole group. The number of patients who died or had serious adverse events, was comparable in the two groups. The rate of abnormal vision was higher in the voriconazole group (22.5% of patients) than in the fluconazole group (7.9% of patients), however, there was no difference in the results of ophthalmologic safety tests between the two groups. The results of this study provided evidence of efficacy in *Candida* infections prior to pursuing the study of voriconazole in the treatment of more invasive *Candida* infections. The Global Comparative Candidemia protocol (608) is an evaluation of voriconazole compared to conventional amphotericin B followed by fluconazole in the treatment of candidemia in non-neutropenic patients. This study protocol was submitted in Feb. 1998 and is ongoing, with over half of the targeted patients (426) enrolled to date.

The pooled efficacy analysis provides summary efficacy information on a total of 91 patients with documented serious systemic *Candida* infection. Of the 91 patients with *Candida* infections, 53 had candidemia and 19 had disseminated infection, with corresponding success rates of 60.4% and 36.8%, respectively. As expected, the success rate in the pooled population was less when voriconazole was used as salvage therapy (51.2%) compared to primary therapy (64.6 %). The results in the pooled efficacy analysis provide additional evidence of the efficacy of voriconazole treatment of infections due to *Candida*.

Voriconazole was also shown to be efficacious in the treatment of fungal infections due to *Scedosporium* and *Fusarium* species. This was especially noteworthy in central nervous system infections due to *Scedosporium*, where successful outcome was seen in seven of 13 patients treated with voriconazole. The outcome for patients with infections due to *Scedosporium* and *Fusarium* species is normally extremely poor and no other antifungal agents are approved for their treatment. The benefit seen with voriconazole against these infections testifies to its high potency in the treatment of infections due to moulds.

In the Empirical Therapy Study (603/MSG42), voriconazole did not fulfill the statistical criteria to show non-inferiority to liposomal amphotericin B as assessed by the composite endpoint. However, voriconazole therapy prevented more breakthrough fungal infections, particularly due to *Aspergillus* species and other filamentous fungi than did therapy with liposomal amphotericin B. This was particularly noteworthy in patients with allogeneic bone marrow transplants and with relapsed leukemia, who are at high risk of developing fungal infections. In terms of safety, with the exception of visual disturbances, adverse events were reported with voriconazole at a similar rate to liposomal amphotericin B. The rates of renal adverse events and hepatic function abnormalities were similar in the two treatment groups, and there was no difference in visual function testing between the two groups. There were fewer elevations in creatinine and infusion related reactions with voriconazole. These efficacy and safety results, when considered in combination with the results of the voriconazole treatment studies, in particular the randomized open label Global Comparative Aspergillosis Study (307/602), support voriconazole being considered an appropriate alternative to liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia.

In addition to safety within the comparative clinical studies, voriconazole safety has also been assessed in pooled populations of healthy volunteers and in patients treated in therapeutic trials and in compassionate use studies. The safety assessment of healthy volunteers who received voriconazole by both oral and intravenous routes shows that adverse events were reported infrequently and infrequently resulted in discontinuation. Assessment of safety in the Therapeutic Studies and Overall Pooled populations shows a similar safety profile to that seen in the three comparative studies.

Assessment of all the available information suggest that the risks associated with voriconazole use include abnormal vision, hepatic function abnormalities, skin reactions and the potential for drug interactions. For other adverse events the relationship to voriconazole treatment is less clear. Abnormal vision is a transient and reversible adverse event that is without long term impact. Hepatic function abnormalities are managed by monitoring the patient's liver function using standard tests of hepatic enzymes and bilirubin. Although the skin reactions rarely disrupt therapy, there may be a photosensitivity aspect to this effect and patients should avoid sunlight if a photosensitivity skin reaction is observed. The potential for drug interactions has been extensively studied and this has enabled provision of practical guidance on their management.

Pharmacokinetic/pharmacodynamic analyses demonstrated statistically significant but weak relationships between plasma voriconazole concentration and the occurrence of liver function test abnormalities. The pharmacokinetic/pharmacodynamic relationship for efficacy was confounded by other medical factors. However, successful outcome was achieved across the range of plasma voriconazole concentrations observed from the dosage regimens studied. The dose regimen of voriconazole studied is likely to represent the top end of the dose-response curve.

In conclusion, voriconazole has been evaluated in an extensive clinical program, and has demonstrated efficacy in the treatment of fungal infections due to *Aspergillus*, *Candida*, *Fusarium* and *Scedosporium* species in immunocompromised patients. Voriconazole was also shown to prevent breakthrough fungal infections in patient populations at high risk of developing fungal infections. The possibility of using both intravenous and oral formulations of voriconazole allows flexibility in patient care and the possibility of prolonged treatment. The clinical studies have identified a number of risks involved with treatment with voriconazole. Abnormal hepatic function is manageable by monitoring the patient. Visual disturbances or skin reactions rarely have an impact on treatment, although patients should avoid sunlight if a photosensitivity skin reaction occurs. The extensive clinical pharmacology program has enabled provision of practical guidance on the management of drug interactions. Overall a favorable benefit: risk profile for voriconazole has been established in the targeted indications.

APPENDIX 1. VORICONAZOLE CLINICAL PHARMACOLOGY PROGRAM

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects		Duration of Intended Treatment
				Entered/ Completed*	PK/Safety	
HUMAN PHARMACOKINETICS						
Oral Single Dose						
202 Single Dose Escalation Solution Study to 4 mg/kg United Kingdom	Completed (Oct 1991)	A single blind, placebo controlled study to investigate the toleration, safety and pharmacokinetics of voriconazole.	Oral voriconazole 0.9 mg/kg 1.5 mg/kg 2.0 mg/kg 4.0 mg/kg Placebo (2 subjects dosed 2x)	 8/7 7/7 7/7 5/5 7/7	 7/8 7/7 7/7 5/5 0/8	Single dose
204 Single Dose Capsule Study United Kingdom	Completed (Feb 1992)	A single blind, placebo controlled, toleration, safety and pharmacokinetics study with voriconazole.	Oral voriconazole 4 mg/kg 5 mg/kg Placebo	 8/8 7/7 6/6	 7/8 7/7 0/6	Single dose
96-501 Single Dose Tablet Study in Japanese Japan	Completed (Sep 1996)	An open, single oral dose, randomized, crossover study.	Voriconazole 100 mg (fasted) 200 mg (fasted) and 200 mg (fed) 300 mg (fasted) 400 mg (fasted)	 6/6 6/6 6/6 6/6	 6/6 6/6 6/6 6/6	 1 day 2 days 1 day 1 day
Oral Multiple Dose						
205 Multiple Dose Capsule Study United Kingdom	Completed (Mar 1992)	A single blind, placebo controlled, single dose study, followed by a 10 day multiple dose study to investigate the pharmacokinetics, safety and toleration of voriconazole.	Oral voriconazole Day 1: QD Days 3-11: q 12 h Day 12: QD 2 mg/kg 4 mg/kg 1.5 mg/kg 2 mg/kg 3 mg/kg Placebo	 8/8 8/8 11/8 8/5 8/8 21/19	 8/8 8/8 8/11 5/8 8/8 0/21	11 days
96-503 Multiple Dose Tablet Study in Japanese Japan	Completed (May 1997)	A single blind, randomized 10 day multiple oral dose study.	Voriconazole 200 mg q 12 h Placebo (matched to 200 mg) q 12 h Voriconazole 300 mg q 12 h Placebo (matched to 300 mg) q 12 h	6/5 3/3 6/6 3/3	5/6 0/3 6/6 0/3	10 days

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects Entered/ Completed*	 PK/Safety	Duration of Intended Treatment
Intravenous Single Dose						
207 Single Dose Escalation IV Study to 4 mg/kg United Kingdom	Completed (Nov 1992)	A single blind, placebo controlled study.	IV voriconazole 0.9 mg/kg 1.5 mg/kg 2.0 mg/kg 2.5 mg/kg 3.0 mg/kg 4.0 mg/kg Placebo	 11/11 10/10 10/10 10/10 5/5 5/5 10/10	 10/11 10/10 10/10 10/10 5/5 5/5 0/10	Single Dose
213 Single Dose Escalation IV Study to 8 mg/kg United Kingdom	Completed (Mar 1993)	A single blind, placebo controlled toleration, safety and pharmacokinetics study.	IV voriconazole 4 mg/kg 6 mg/kg 8 mg/kg Placebo (three subjects were dosed twice)	 9/9 9/9 6/6 9/9	 9/9 9/9 6/6 0/9	Single dose
96-502 Single Dose IV Study in Japanese Japan	Completed (Dec 1996)	An open, single dose intravenous study with three consecutive dose groups.	IV voriconazole 1.5 mg/kg 3.0 mg/kg 6.0 mg/kg	 6/6 6/6 6/6	 6/6 6/6 6/6	1 day
226 Escalating Dose Voriconazole and SBECD Study United Kingdom	Completed (Aug 1994)	A single blind, randomized, 3 period crossover, intravenous dose escalation study.	IV voriconazole 3 mg/kg with: CP-217,861-02 48 mg/kg IV Voriconazole 6 mg/kg with: CP-217,861-02 96 mg/kg CP-217,861-02 50 mg/kg CP-217,861-02 100 mg/kg	 9/9 8/8 3/3 5/5	 8/9 8/8 0/3 0/5	Single 1 hour IV dose
Intravenous Multiple Dose						
214 Multiple Dose IV Study at 3 mg/kg q 12 h United Kingdom	Completed (Mar 1993)	A single blind, placebo controlled toleration, safety and pharmacokinetics study.	IV voriconazole: Day 1: 3 mg/kg QD Days 3-11: 3 mg/kg q 12 h Day 12: 3 mg/kg QD Placebo Day 1: QD Days 3-11: q 12 h Day 12: QD	9/9 3/3	9/9 0/3	11 days

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects Entered/ Completed*	 PK/Safety	Duration of Intended Treatment
227 Loading Dose Voriconazole and SBECD Study United Kingdom	Completed (Nov 1994)	A single blind, placebo controlled, multiple dose, intravenous study. Part A: safety, toleration and pharmacokinetics. Part B: open radiolabel study for safety, toleration and pharmacokinetics.	Part A IV voriconazole Day 1: 6 mg/kg with 96 mg/kg CP-217,861-02 q 12 h Days 2 to 9: 3 mg/kg with 48 mg/kg CP-217,861-02 q 12 h Day 10: 3 mg/kg with 48 mg/kg CP-217,861-02 QD Placebo Part B Day 1: [^{14}C]-CP-217, 861-02 Days 2-9: 50 mg/kg CP-217-861-02 Day 10: [^{14}C]-CP-217,861-02	 9/9 9/9 9/9	 9/9 9/9 9/9	10 days
97-501 Multiple Dose IV Study in Japanese Japan	Completed (July 1997)	A single blind, placebo controlled multiple dose intravenous study.	IV voriconazole: Step 1 Day 1: 3 mg/kg QD Day 3: 6 mg/kg q 12 h Days 4-11: 3 mg/kg q 12 h Day 12: 3 mg/kg QD Step 2 (single dose) Day 1: 4 mg/kg QD Step 2 (multiple dose) Day 1: 6 mg/kg q 12 h Days 2-9: 4 mg/kg q 12 h Day 10: 4 mg/kg QD Placebo: Step 1 Step 2	 6/6 11/11 6/6 3/2 3/2	 6/6 11/11 6/6 0/3 0/3	 11 days 1 day 10 days 11 days 10 days

Study Number **Title** **Location of Sites**	**Completion Status** **(start date)**	**Design**	**Treatment**	**Number of subjects**		**Duration of Intended Treatment**
				Entered/ Completed*	**PK/Safety**	
Oral and Intravenous						
230 Multiple Dose Escalation IV/Oral Switch Study Belgium	Completed (July 1996)	A randomized, double blind, placebo controlled, dose escalation and intravenous to oral switchover study in two cohorts using voriconazole and sulfobutylether-• -cyclodextrin (SBECD).	Cohort 1 Period 1			
			Voriconazole Day 1: 6 mg/kg IV q 12 h Days 1-7: 3 mg/kg IV q 12 h Days 8-14: 200 mg oral q 12 h or	14/14	14/14	14 days
			IV placebo (SBECD) Oral placebo	14/14	0/14	
			Cohort 1 Period 2			
			Voriconazole Day 1: 6 mg/kg IV q 12 h Days 1-7: 5 mg/kg IV q 12 h Days 8-14: 400 mg oral q 12 h	14/13	14/14	
			IV placebo (SBECD) Oral placebo	14/14	0/14	
			Cohort 2			
			Voriconazole Day 1: 6 mg/kg IV q 12 h Days 1-7: 4 mg/kg IV q 12 h Days 8-14: 300 mg oral q 12 h	7/7	7/7	
			SBECD			
			IV placebo (SBECD) Oral placebo	7/7	0/7	
Radiolabel Study						
220 Radiolabelled Oral and IV Study The Netherlands	Completed (Feb 1994)	An open, parallel group study to investigate the absorption, metabolism and excretion of [^{14}C]-voriconazole.	Oral voriconazole Days 1-10 (except Day 6 am): 200 mg q 12 h Day 6 AM dose: [^{14}C]; 170 mg	3/3	3/3	10 days
			IV voriconazole Days 1-10 (except Day 6 am): 3 mg/kg q 12 h Day 6 AM dose: [^{14}C]; 3 mg/kg	3/3	3/3	
Study with Patients						
673 Multiple Dose Adult Patient Pharmacokinetic Study United States	Completed (May 1996)	A randomized, double blind, active controlled safety, tolerance and pharmacokinetics study in patients at risk for aspergillosis.	Oral voriconazole 200 mg q 12 h	9/9	9/9	14 days
			Oral fluconazole 400 mg QD	6/5	6/6	
			Oral voriconazole 300 mg q 12 h	9/9	9/9	

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects Entered/ Completed*	 PK/Safety	Duration of Intended Treatment
PHARMACOKINETIC STUDIES IN POPULATION SUBSETS						
Renal Impairment						
237 Single Dose Renal Impairment Study United Kingdom	Completed (Sep 1997)	An open, single dose, parallel group, pharmacokinetics, safety and toleration study in subjects with impaired renal function.	Voriconazole 200 mg QD oral tablet: Normal renal function Mild renal impairment Moderate renal impairment Severe renal impairment	 6/6 6/6 6/6 6/6	 6/6 6/6 6/6 6/6	Single dose
Hepatic Impairment						
238 Single Dose Hepatic Impairment Study Germany	Completed (Oct 1997)	An open, single dose pharmacokinetics, safety and toleration study in subjects with hepatic cirrhosis and healthy subjects.	Voriconazole 200 mg QD oral tablet: Healthy subjects Cirrhotic subjects	 12/12 12/12	 12/12 12/12	Single dose
1012 Multiple Dose Hepatic Impairment Study France Germany	Completed (May 2000)	An open, multiple dose pharmacokinetics, safety and toleration study in subjects with hepatic impairment and healthy subjects.	Oral voriconazole Healthy subjects Day 1: 400 mg q 12 h Days 2-6: 200 mg q 12 h Day 7: 200 mg in AM Cirrhotic subjects Day 1: 200 mg q 12 h Days 2-6: 100 mg q 12 h Day 7: 100 mg in AM	 6/6 6/6	 6/6 6/6	7 days
Pediatrics						
249 Single Dose Pediatric Study United Kingdom	Terminated (Jun 1999)	An open, multicenter, single dose pharmacokinetics, safety and toleration study in immunocompromised children aged 2-11 yrs.	IV voriconazole 3 mg/kg 4 mg/kg 6 mg/kg (Not done)	 6/6 5/5 Not done	 6/6 5/5 Not done	One infusion over 1 hour
Elderly						
250 Male/Female and Young/Elderly Study France	Completed (Mar 1999)	An open parallel group pharmacokinetics, safety and toleration study in young and elderly.	Voriconazole IV Day 1: 6 mg/kg once Voriconazole Oral Day 1: 400 mg q 12 h Days 2-6: 200 mg q 12 h Day 7: 200 mg QD Young males Elderly males Young females Elderly females	 18/18 18/18 18/18 18/17	 18/18 18/18 18/18 18/18	IV: Single Dose Oral: 7 days

Study Number **Title** **Location of Sites**	**Completion Status** **(start date)**	**Design**	**Treatment**	**Number of subjects**		**Duration of Intended Treatment**
				Entered/ Completed*	**PK/Safety**	
Food Effect						
217 Single Dose Fed/Fasted Solution Study Belgium	Completed (July 1993)	An open, randomized, two way crossover study.	Voriconazole oral solution, 200 mg single dose After overnight fast After food	 14/14 15/15	 14/14 14/15	 Single dose Single dose
222 Multiple Dose Fed/Fasted Tablet Study Belgium	Completed (Nov 1993)	An open, multiple dose, randomized, two way crossover pharmacokinetics study.	Voriconazole Day 1: 200 mg q 12 h Day 7: 200 mg QD Fasted Fed	 12/12 12/12	 12/12 12/12	7 days
96-501: See above for details						
1005: See above for details						

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects: Entered/ Completed*	Number of subjects: PK/Safety	Duration of Intended Treatment
DRUG INTERACTION STUDIES						
228 Rifampicin/ Rifabutin on Voriconazole Interaction Study Belgium	Completed (Mar 1995)	An open, randomized, placebo controlled, parallel group study, to investigate the effects of multiple dose rifampicin and rifabutin on the steady state pharmacokinetics of voriconazole.	Voriconazole: Days 1-6: 200 mg q 12 h Day 7: 200 mg QD Days 15-20: 200 mg q 12 h Day 21: 200 mg QD plus rifampicin 600 mg QD Days 8-30 or rifabutin 300 mg QD Days 8-30 or Placebo Days 8-21: QD Days 24-30: Voriconazole 400 mg q 12 h plus rifampicin Days 24-30: 300 or 350 mg voriconazole q 12 h plus rifabutin	8/8 8/6 7/7	8/8 7/8 7/7	30 days 30 days 21 days
229 Cimetidine/Ranitidine on Voriconazole Interaction Study Belgium	Completed (Jan 1996)	An open, randomized, placebo controlled, three way crossover study to investigate the effects of multiple dose cimetidine and ranitidine on the steady state pharmacokinetics of voriconazole.	Oral voriconazole Days 1-6: 200 mg q 12 h Day 7: 200 mg QD Plus cimetidine Days 1-6: 400 mg q 12 h Day 8: 400 mg QD Plus ranitidine Days 1-6: 150 mg q 12 h Day 8: 150 mg QD Plus placebo	13/12 12/12 13/12	11/13 12/12 12/13	8 days

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects Entered/ Completed*	 PK/Safety	Duration of Intended Treatment
233 Phenytoin on Voriconazole Interaction Study United Kingdom	Completed (Sep 1996)	An open, placebo controlled, parallel group study to investigate the effects of multiple dose phenytoin on the steady state pharmacokinetics of voriconazole.	Oral voriconazole Day 1: 200 mg q 6 h Days 2-6: 200 mg q 12 h Day 7: 200 mg QD Day 15: 200 mg q 6 h Days 16-21: 200 mg q 12 h Day 22-27: 400 mg q 12 h Day 28: 400 mg QD Plus phenytoin Days 8-28: 300 mg QD Plus placebo Days 8-21	12/7 12/11	10/12 11/12	Voriconazole 21 days Phenytoin 21 days Placebo 14 days
240 Indinavir on Voriconazole Interaction Study Belgium	Completed (Jun 1997)	An open, placebo controlled, parallel group study to investigate the effects of multiple dose indinavir on the steady state pharmacokinetics of voriconazole.	Voriconazole Days 1-17: 200 mg q 12 h Plus indinavir Days 8-17: 800 mg q 8 h Plus placebo Days 8-17: q 8 h	9/8 9/9	8/9 9/9	Voriconazole 17 days Indinavir/ Placebo 10 days 10-day extension not conducted
243 Erythromycin/ Azithromycin on Voriconazole Interaction Study Belgium	Completed (Jan 1998)	An open, randomized, placebo controlled, parallel group study to investigate the effect of erythromycin and azithromycin on the steady state pharmacokinetics of voriconazole.	Voriconazole Days 1-13: 200 mg q 12 h Day 14: 200 mg QD Plus erythromycin Days 8-13: 1g q 12 h Day 14: 1g QD Plus azithromycin Days 12-14: 500 mg QD Plus placebo Days 8-14	10/10 10/10 10/10	10/10 10/10 10/10	Erythromycin 7 days Azithromycin 3 days Placebo 7 days

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects		Duration of Intended Treatment
				Entered/ Completed*	PK/Safety	
247 Loading Dose/ Omeprazole on Voriconazole Interaction Study Belgium	Completed (Jun 1998)	An open, placebo controlled, randomized, two way crossover study to investigate the effects of multiple dose omeprazole on the steady state pharmacokinetics of voriconazole.	Voriconazole, oral tablets Day 1: 400 mg q 12 h Days 2-9: 200 mg q 12 h Day 10: 200 mg QD Day 10 Plus omeprazole, oral capsules Days 1-10: 40 mg QD Plus placebo Days 1-10	18/17 17/17	17/18 17/17	10 days
001 Voriconazole on Tacrolimus Interaction Patient Study United States	Terminated (Feb 1999)	An open, randomized, two way crossover, multicenter study with voriconazole and tacrolimus in hepatic transplant patients.	Tacrolimus + voriconazole (200 mg q 12 h) Tacrolimus + placebo	1/0 1/0	0/1 0/1	7 days
210 Voriconazole On Prednisolone Interaction Study Belgium	Completed (Mar 1993)	A double blind, placebo controlled, multiple dose pharmacokinetics, safety and toleration study with voriconazole and prednisolone.	Prednisolone Days 1 and 24: 60 mg QD Plus voriconazole Days 4-32: 200 mg q 12 h Day 33: 200 mg QD Plus voriconazole Days 4-32: 250 mg QD AM and Placebo QD PM Day 33: 250 mg QD AM Plus placebo Days 4-33	6/6 6/6 7/6	6/6 6 /6 6/7	Prednisolone 2 days Voriconazole 30 days
235 Voriconazole on Cyclosporine Interaction Study Sweden UK France	Completed (Jan 1997)	A double blind, randomized, two period, two treatment, placebo controlled, crossover study with voriconazole and cyclosporine in renal transplant patients.	Voriconazole Days 1-7: 200 mg q 12 h Day 8: 200 mg QD Plus cyclosporine Days 1-8: maintenance dose Plus placebo	14/7 11/11	7/14 7/11	8 days
236 Voriconazole on Digoxin Interaction Study Belgium	Completed (Mar 1997)	A double blind, randomized, placebo controlled, parallel group study to investigate the effects of voriconazole on the steady state pharmacokinetics of digoxin in healthy male volunteers.	Digoxin Day 1: 0.5 mg q 12 h, Day 2: 0.25 mg q 12 h Days 3-22: 0.25 mg QD Plus voriconazole Days 11-22: 200 mg q 12 h Plus placebo Days 11-22: q 12 h	12/12 13/12	12/12 12/13	22 days`

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects		Duration of Intended Treatment
				Entered/ Completed*	PK/Safety	
239 Voriconazole On Warfarin Interaction Study Belgium	Completed (Jan 1997)	A double blind, randomized, placebo controlled, two way crossover study with voriconazole and warfarin.	Voriconazole Days 1-12: 300 mg q 12 h Plus warfarin 30 mg on Day 7 Placebo Days 1-12 q 12 h Plus warfarin 30 mg on Day 7	17/14 15/13	13/16 13/15	Voriconazole 12 days Warfarin 1 day
241 Voriconazole on Phenytoin Interaction Study United Kingdom	Completed (Sep 1997)	A parallel group, double blind, placebo controlled study with voriconazole and phenytoin.	Phenytoin Day 1: Loading dose based on body weight Days 2-17: 300 mg QD Plus voriconazole Days 8 –17: 400 mg q 12 h Plus placebo	 11/6 11/9	 6/11 9/11	Voriconazole 10 days Phenytoin 17 days
244 Voriconazole on Indinavir Interaction Study United Kingdom	Completed (Jan 1998)	A double blind, randomized, two way cross over study with voriconazole and indinavir.	Indinavir oral tablets Days 1-6: 800 mg q 8 h Day 7: QD Plus voriconazole oral tablets Days 1-7: 200 mg q 12 h Plus placebo Days 1-7	 14/14 16/14	 14/14 14/16	7 days
1009 Voriconazole on Tacrolimus Interaction Study United Kingdom	Completed (Jan 2000)	A single blind, randomized, placebo controlled two period crossover study to investigate the effect of voriconazole on the pharmacokinetics of tacrolimus.	Tacrolimus Day 6: 0.1 mg/kg in the AM Plus voriconazole Day 1: 400 mg q 12 h Days 2-5: 200 mg q 12 h Day 6: 200 mg in the AM Plus placebo Days 1-6	 14/12 14/14	 12/12 12/14	Tacrolimus 1 day Voriconazole 6 days
1013 Voriconazole on Omeprazole Interaction Study United Kingdom	Completed (Mar 2000)	A double blind, randomized, placebo controlled, two period crossover study with voriconazole and omeprazole.	Omeprazole Days 1-7: 40 mg QD plus Plus voriconazole oral Day 1: 400 mg q 12 h Days 2-6: 200 mg q 12 h Plus placebo Days 1-6 q 12 h	 16/16 16/16	 16/16 16/16	7 days

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects: Entered/ Completed*	Number of subjects: PK/Safety	Duration of Intended Treatment
HUMAN PHARMACODYNAMICS						
231 Single Dose Visual Function Study France	Completed (Jun 1996)	A randomized, double blind, placebo controlled, crossover study with IV voriconazole to investigate electrophysiological changes in the retina and visual cortex.	Voriconazole 8 mg/kg IV Placebo IV	8/8 8/8	8/8 8/8	1 hour IV infusion
PHARMACOGENETICS						
242 Retrospective Phenotyping and Genotyping Study Belgium UK	Completed (Aug 1997)	An open, retrospective study to determine the CYP450-2C19 genotype and phenotype status of subjects who have previously received voriconazole whilst participating in a Phase I clinical study.	Not applicable (No study drug was given in this study. Subjects received a single oral capsule of omeprazole for CYP2C19 phenotyping.)	127/127	0/127	Single dose of omeprazole
97-502 Retrospective Genotyping Study in Japanese (Oral) Japan	Completed (Oct 1997)	A non treatment study to investigate the genetic polymorphism of CYP2C19.	Subjects received oral voriconazole in Study 96-501; no study drugs were administered in this study.	24/24	Genotype analyzed in 24 subjects	Not applicable
97-503 Retrospective Genotyping Study in Japanese (IV) Japan	Completed (Oct 1997)	A non treatment study to investigate the genetic polymorphism of CYP2C19.	Subjects received IV voriconazole in Study 96-502; no study drugs were administered in this study.	11/11	Genotype analyzed in 11 subjects	Not applicable
SUPPORTIVE STUDIES—SAFETY SUMMARY REPORTS						
216 Single Dose Capsule and IV Study Italy	Completed (Oct 1993)	A pilot, open, parallel group, pharmacokinetics, safety and toleration study with voriconazole.	Voriconazole 200 mg oral capsule single dose 200 mg IV single dose	 11/11 12/11	 0/1 0/12	 Single dose Single dose
201 Single Dose Escalation Solution Study to 0.9 mg/kg United Kingdom	Completed (Aug 1991)	A single blind, placebo controlled dose escalation study with two cohorts of healthy male volunteers.	Cohort A Oral voriconazole 0.06 mg/kg 0.3 mg/kg Placebo Cohort B Oral voriconazole 0.125 mg/kg 0.6 mg/kg 0.9 mg/kg Placebo	 9/9 7/7 8/8 8/9 8/8 5/5 9/9	 0/9 0/7 0/8 0/9 0/8 0/5 0/9	Single dose

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects Entered/ Completed*	Number of subjects PK/Safety	Duration of Intended Treatment
206 Single Dose Escalation Iv Study to 0.9 mg/kg United Kingdom	Completed (Jun 1992)	A single blind, placebo controlled dose escalation study in healthy male volunteers.	IV voriconazole 0.2 mg/kg 0.4 mg/kg 0.6 mg/kg 0.9 mg/kg Placebo (excipient) Placebo (saline)	 13/12 11/11 11/11 6/6 12/11 12/12	 0/13 0/11 0/11 0/6 0/12 0/12	Single dose
209 Multiple Dose IV Study at 0.9 mg/kg q 8 h United Kingdom	Completed (Jan 1993)	A single blind, placebo controlled, single dose study followed by a ten day multiple dose study with voriconazole.	IV voriconazole 0.9 mg/kg QD 0.9 mg/kg q 8 h for 10 days Placebo Single dose q 8 h for 10 days	9/9 3/3	0/9 0/3	Single dose followed by 10 days
208 Single Dose Fed/Fasted Capsule Study United Kingdom	Completed (Oct 1992)	An open, randomized, two way, crossover pharmacokinetics, safety and toleration study.	Voriconazole 200 mg oral QD (fasted) 200 mg oral QD (fed)	 17/15 17/16	 0/15 0/16	Single dose
234 Voriconazole on Warfarin Interaction Supportive Study Belgium	Terminated (Sep 1996)	A double blind, randomized, placebo controlled, two way crossover study with oral voriconazole and warfarin.	Study Period 1 Days 1-12: voriconazole 300 mg q 12 h Day 7: warfarin 40 mg QD Study Period 1 Days 1-12: Placebo Day 7: warfarin 40 mg QD Study Period 2 Not conducted	7/0 7/0	0/7 0/7	Voriconazole 12 days Warfarin 1 day
SBECD STUDY						
225 Single Dose Escalation SBECD Study United Kingdom	Completed (Jul 1994)	A single blind, placebo controlled toleration and safety study with sulfobutylether-• - cyclodextrin (SBECD).	SBECD 25 mg/kg IV 50 mg/kg IV 100 mg/kg IV 200 mg/kg IV Placebo IV	 10/10 10/10 10/10 10/10 10/10	 0/10 0/10 0/10 0/10 0/10	1 hour infusion
STUDIES SUBMITTED DURING REVIEW PERIOD						
1004 Multiple Dose Visual Function Study France	Completed (Mar 2000)	A double blind, randomized placebo controlled, parallel group study to investigate the effect of multiple oral doses of voriconazole on visual function in healthy male subjects. 36 subjects were evaluated for pharmacodynamics.	Oral voriconazole Day 1: 400 mg q 12 h Days 2-28: 300 mg q 12 h Day 29: 300 mg QD Oral placebo Days 1-28: q 12 h Day 29: QD	18/17 18/17	18/18 18/18	Voriconazole 29 days Placebo 29 days

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects Entered/ Completed*	 PK/Safety	Duration of Intended Treatment
1007 Multiple Dose Pediatric Study United States United Kingdom Costa Rica Panama	Completed (Jul 2000)	An open, intravenous, multiple dose, multicenter study to investigate the pharmacokinetics, safety and toleration of voriconazole in children aged 2-12 years who require treatment for the prevention of systemic fungal infection.	IV voriconazole Day 1: 6 mg/kg q 12h Days 2-3: 3 mg/kg q12h Day 4 AM only: 3 mg/kg Day 4 PM only: 4 mg/kg Days 5-7: 4 mg/kg q 12h Day 8: 4 mg/kg	28/19	28/28	8 days
1011 Hemodialysis Study United States	Completed (Oct 2000)	An open, parallel group study to investigate the effect of hemodialysis on the pharmacokinetics and safety of SBECD and voriconazole following multiple oral dosing in subjects with renal failure.	IV voriconazole Hemodialysis patients Day 1: 6 mg/kg q 12h Days 2-4: 3 mg/kg q 12h Day 5 AM only: 3 mg/kg Healthy subjects Day 1: 6 mg/kg q 12h Days 2-4: 3 mg/kg q 12h Day 5 AM only: 3 mg/kg	 8/6 6/6	 7/8 6/6	5 days
1014 Voriconazole on Mycophenolate Interaction Study United Kingdom	Completed (Aug 2000)	A single blind, randomized, placebo controlled, two period crossover study to investigate the effect of voriconazole on the pharmacokinetics of mycophenolic acid.	Mycophenolate mofetil Day 4: 1 g in the AM Plus voriconazole Day 1: 400 mg q 12 h Days 2-5: 200 mg q 12 h Plus placebo Days 1-5: q 12 h	 14/13 14/14	 13/14 14/14	5 days
1015 Voriconazole on Sirolimus Interaction Study United Kingdom	Completed (Jun 2000)	A single blind, randomized, placebo controlled, two period crossover study to investigate the effect of voriconazole on the pharmacokinetics of sirolimus.	Sirolimus Day 4: 2 mg in the AM Plus voriconazole Day 1: 400 mg q 12 h Days 2-9: 200 mg q 12 h Plus placebo Days 1-9 q 12 h	 8/8 8/7	 8/8 7/8	9 days
1016 Multiple Dose Renal Impairment Study Belgium France Germany	Completed (Mar 1999)	An open, parallel group, multicenter study to determine the effects of impaired renal function on the pharmacokinetics, safety and toleration of voriconazole and SBECD following multiple IV dosing.	IV voriconazole Moderate renal impairment Day 1: 6 mg/kg q 12h Days 2-7: 3 mg/kg q 12h Normal subjects Day 1: 6 mg/kg q 12h Days 2-7: 3 mg/kg q 12h	 7/6 6/6	 6/7 6/6	7 days

Study Number Title Location of Sites	Completion Status (start date)	Design	Treatment	Number of subjects		Duration of Intended Treatment
				Entered/ Completed*	PK/Safety	
1024 Two Way Rifabutin/Voriconazole Interaction Study Belgium	Completed (Oct 2000)	A single blind, randomized, placebo controlled, parallel group study to investigate the effects of multiple dose rifabutin on the steady state pharmacokinetics of voriconazole.	Group A: Day 1: voriconazole 400 mg q 12 h Days 2-7: voriconazole 200 mg q 12 h Days 8-14: rifabutin 300 mg QD Days 15-21: voriconazole 400 mg q 12 h plus rifabutin 300 mg QD	12/10	10/12	21 days
			Group B: Day 1: voriconazole 400 mg q 12 h Days 2-7: voriconazole 200 mg q 12 h Days 8-14: placebo QD Day 15: voriconazole 400 mg q 12 h Days 16-21: voriconazole 200 mg q 12 h plus placebo QD	12/12	12/12	
			Group C: Days 1-7: placebo q 12 h Days 8-14: rifabutin 300 mg QD Days 15-21: placebo q 12 h plus rifabutin 300 mg q 12 h	12/9	9/12	
OTHER STUDIES						
1019 Suspension Bioequivalence Study United Kingdom	Completed	An open, three period crossover, multiple dose study to investigate the bioequivalence of the suspension (fed/fasted) *vs.* the tablet	Suspension fasted Tablet fasted Suspension fed Day 1: 400 mg bid Days 2-7: 200 mg bid	N/A	N/A	3 periods of 7 days
1021 Single Dose Comparative QTc Study #1	Terminated	A double blind, placebo controlled, double dummy, five-way crossover,dose escalation study with random insertion of ketoconazole and placebo to investigate the effect of intravenous voriconazole on QTc interval	IV voriconazole 4 mg/kg IV voriconazole 8 mg/kg IV voriconazole 12 mg/kg Ketoconazole 800 mg Placebo	N/A	N/A	Single dose

Study Number **Title** **Location of Sites**	**Completion Status** **(start date)**	**Design**	**Treatment**	**Number of subjects**		**Duration of Intended Treatment**
				Entered/ Completed*	**PK/Safety**	
1022 Single and Multiple Oral Dose Study in Japan	Ongoing (Oct. 2000)	A open label single dose and 7 day multiple oral dose study with the commercial formulation tablet	Oral voriconazole: Group 1 (EM/HEM) Day 1: PO 200 mg single dose Day 5: PO 400 mg bid Days 6-11: PO 200 mg bid Group 2 (EM/HEM) Day 1:PO 300 mg single dose Day 5: PO 400 mg bid Days 6-11: PO 300 mg bid Group 3 (PM) Day 1:PO 200 mg single dose Day 5: PO 400 mg bid Days 6-11: PO 200 mg bid	N/A	N/A	8 days

bid = twice daily; EM = extensive metabolizer; HEM = heterozygous extensive metabolizer; IV = intravenous; N/A = not available; PK = pharmacokinetics; PM = poor metabolizer; PO = orally; QD = once daily

*Denominator indicates the number of subjects completing the study or dosing period as appropriate to the study.

APPENDIX 2. VORICONAZOLE CLINICAL STUDIES

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
Aspergillosis										
307/602 Global Comparative Aspergillosis Study U.S.; Canada; Europe; Israel; Mexico So. America; India; Australia	307: Jul 1997 / Feb 2001 602 : Sep 1997 / Jan 2001	OL, MC, randomized, comparative study of voriconazole versus amphotericin B followed by OLAT in immunocompromised patients with acute invasive aspergillosis	Voriconazole (V) IV 6 mg/kg q 12 h x 2 doses → 4 mg/kg q 12 h x 7 d → voriconazole PO 200 mg bid Dose escalation to 6 mg/kg q 12 h IV and 300 mg bid PO permitted Amphotericin B (A) 1.0-1.5 mg/kg/d x 2 wk Dose adjustment permitted for toxicity Both groups could be switched to OLAT if failed to respond or unable to tolerated IRT Total duration maximum 12 wk	V 196/79* A 185/7	ITT MITT PP	V 194 A 185 V 144 A 133 V 131 A 111	Global success Survival	Safety	V 196 A 185	Adverse events Discontinuations Laboratory analyses
304 Non-Comparative Aspergillosis Study Europe	Jan 1994 / Jul 1996	OL, MC, uncontrolled study of IV and oral voriconazole in immunocompromised patients with acute invasive aspergillosis with or without previous anti-fungal treatment	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 3 mg/kg q 12 h x 7-28 d → voriconazole PO 200 mg bid Total duration 4-24 wk	137/33	ITT PP Expert Eval	137 101 112	Clinical response Mycology Survival	Safety	137	Adverse events Discontinuations Laboratory analyses

Study Number Title Location of sites	**Start/end dates**	**Design**	**Treatments**	**Entered (or randomized and received study drug)/ completed**	**Efficacy**			**Safety**		
					Efficacy population(s)#		**Efficacy endpoints**	**Safety population(s)**		**Safety endpoints**
1003 Historical Control Study U.S.; Europe	Jan 1993 / Dec 1995	Historical control survey to collect global response and survival data for immunocompromised patients who received standard therapy for invasive aspergillosis	Standard therapy	257	Eval	257	Clinical response Survival	N/A	N/A	N/A
304 *vs.* 1003		Comparison of matched populations from 304 and 1003 to compare global response and survival in patients with invasive aspergillosis			10pp 5pp	304 / 72 1003 / 126; 304 / 50 1003 / 92	Clinical response Survival	N/A	N/A	N/A
303 Chronic Fungal Infection Study Europe	Jul 1993 / Dec 1996	OL, MC, uncontrolled study of voriconazole in patients with chronic fungal infections	Voriconazole 200 mg PO bid (100 mg bid if <40 kg). Dose escalation to 350 mg bid permitted based on clinical response	58/18	ITT PP	58 46	Clinical response	Safety	58	Adverse events Discontinuations Laboratory analyses
Empirical Treatment										
603 Empirical Therapy Study; U.S.; Canada; Europe; India	Mar 1998 / Sep 1999	OL, MC, comparison on voriconazole with liposomal amphotericin B in the empirical treatment of immunocompromised patients with persistent fever and neutropenia	Voriconazole (V) IV 6 mg/kg q 12 h x 2 doses → 3 mg/kg q 12 h x 3 d → 200 mg PO bid Liposomal amphotericin B (A) IV 3 mg/kg/d Total duration up to 12 wk	V 421/310 A 428/335	ITT MITT PP	V 421 A 428 V 415 A 422 V 382 A 368	Overall response: Survival Absence of BT infections, Defervescence, Lack of discontinuation due to toxicity/lack of efficacy	Safety	V 421 A 428	Adverse events Discontinuations Laboratory analyses

Study Number **Title** **Location of sites**	**Start/end dates**	**Design**	**Treatments**	**Entered (or randomized and received study drug)/ completed**	**Efficacy**			**Safety**		
					Efficacy population(s)#		**Efficacy endpoints**	**Safety population(s)**		**Safety endpoints**
Rare and Refractory Infections										
309/604 Global Rare and Refractory Study U.S.; Canada; Europe; Australia; Thailand	Dec 1997 / Oct 2000 <u>309:</u> Efficacy cut-off date: 31 May 1999 <u>604:</u> Efficacy cut-off date: 26 May 1999 <u>309 and 604:</u> Safety cut-off date: 1 May 2001	OL, noncomparative studies of voriconazole in patients with systemic and invasive fungal therapy for which there is no licensed therapy and the treatment of systemic or invasive fungal infections in patients failing or intolerant of treatment with approved anti-fungal agents	Voriconazole IV 6 mg/kg q 12 h x 24 h → 4 mg/kg q 12 h x 3 d Voriconazole PO 400 mg q 12 h x 1 d → 200 mg q 12 h Total duration 12 wk	309: 166 / 73 604: 206 / 94	MITT	37 111	Clinical response	Safety	166 206	Adverse events Discontinuations Laboratory analyses
Candidiasis										
302 Dose Ranging Oropharyngeal Candidiasis Study Europe	Jan 1993 / Feb 1994	DB, randomized, MC dose-ranging study of oral voriconazole in HIV positive patients with oropharyngeal candidiasis	Voriconazole 50 mg PO QD Voriconazole 200 mg PO QD Voriconazole 200 mg PO bid Total duration 7 d Post-treatment option to switch to fluconazole 50 mg PO QD for additional 7 d	167/127	ITT	167	Clinical response Mycology Voriconazole plasma levels	Safety	167	Adverse events Discontinuations Laboratory analyses
305 Esophageal Candidiasis Study Europe; Australia Russia Singapore; South Africa; Thailand	Sep 1995 / Jan 1999	DB, randomized, MC comparative study of voriconazole vs. fluconazole in the treatment of esophageal candidiasis	Voriconazole (V) 200 mg PO q 12 h Fluconazole (F) 400 mg PO qd x 1 d → 200 mg PO QD Total duration 2-6 wk	V 200/131 F 191/1136	ITT PP	V 200 F 191 V 115 F 141	Success Esophagoscopy Symptoms	Safety	V 200 F 191	Adverse events Discontinuations Laboratory analyses

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
608 Comparative Candidemia Study U.S.; Europe; So. America; Canada; Israel; Morocco; So. Africa	Sep 1998 / Safety cut-off date: 1 May 2001	OL, MC, randomized comparative study of voriconazole (V) *vs.* conventional amphotericin B (A) followed by fluconazole in the treatment of candidemia in non-neutropenic patients,	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 3 mg/kg q 12 h Day 4 or later: Voriconazole 200 mg bid (patients >40 kg) or 100 mg bid (patients ≤40 kg) Dose escalations permitted to 4 mg/kg IV or 300 mg PO bid in case of insufficient clinical response Amphotericin B 0.7 mg/kg/day x 3-7 days → fluconazole IV or oral, minimum dose of 400 mg/day Total duration: dosing to be continued until 2 wks after infection resolved.	V 110/40 A 52/20	N/A	N/A	Clinical response Mycology	Safety	V 110 A 52	Adverse events Discontinuations Laboratory analyses
Compassionate Use and Extension Studies										
301 Non-US Compassionate Program Europe; Australia; Canada; Czech Republic; Iceland; Israel; Saudi Arabia; Singapore	Mar 1997 / Efficacy cut-off date: 20 Sep 1999 Safety cut-off date: 1 May 2001	Named patients program for patients with proven life-threatening invasive fungal infections who are failing or are intolerant of currently available anti-fungal therapies	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 4 mg/kg q 12 h <u>or</u> Voriconazole 400 mg/bid on day 1 → 200 mg/bid (patients > 40 kg) Voriconazole 200 mg/bid on day 1 → 100 mg/bid (patients < 40 kg) Dose escalations were allowed in cases of insufficient clinical response	288/83 7 ongoing at safety cut-off date	ITT	127	Global response	Safety	288	Adverse events Discontinuations Selected laboratory analyses

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
303A & 304A Named Patient Use Of Voriconazole Europe	Jul 1993 / Sep 1997 Cutoff 1 May 2001	Named patients program for patients with proven life-threatening invasive fungal infections who are failing or are intolerant of currently available anti-fungal therapies	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 3 mg/kg q 12 h x 7-28 d → voriconazole PO 200 mg bid	46/14	ITT	46	Global response	Safety	46	Adverse events Discontinuations Laboratory analyses
311 and 607 Non-Comparative Extension Study of Invasive Fungal Infections US; Canada; Argentina; Europe; Australia	May 1998 / Efficacy cut-off date: 20 Sep 1999 Safety cut-off date: 1 May 2001	OL, extension protocol for patients with invasive fungal infections previously treated with voriconazole in a Phase 3 study requiring more than 16 wks of treatment	Voriconazole 200-300 mg PO bid or 3-4 mg/kg q 12 h IV for patients ≥40 kg and 100-150 mg bid for patients <40kg	91/45 7 ongoing at safety cut-off date	ITT	33	Global response Mycology	Safety	91	Adverse events Discontinuations Laboratory analyses
312 Emergency Use Protocol in Europe	Jul 1998 / Efficacy cut-off date: 20 Sep 1999 Safety cut-off date: 1 May 2001	Emergency use protocol for patients with proven life-threatening invasive fungal infections who are failing or are intolerant of currently available anti-fungal therapies	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 4 mg/kg q 12 h → voriconazole PO 200 mg bid (patients > 40 kg) or 100 mg bid (patients < 40 kg) Dose escalations and reductions were allowed in cases of insufficient clinical response or intolerance, respectively	37/9 6 ongoing at Safety cut-off date	ITT	7	Global response	Safety	37	Adverse events Discontinuations Selected laboratory analyses

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
606 Emergency Use Protocol in US & Canada	Sep 1997 / Efficacy cut-off date: 20 Sep 1999 Safety cut-off date: 1 May 2001	Emergency use protocol for patients with proven life-threatening invasive fungal infections who are failing or are intolerant of currently available anti-fungal therapies	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 4 mg/kg q 12 h → voriconazole PO 200 mg bid (patients > 40 kg) or 100 mg bid (patients < 40 kg) Dose escalations and reductions were allowed in cases of insufficient clinical response or intolerance, respectively	134/18 16 ongoing at Safety cut-off date	ITT	52	Global response	Safety	134	Adverse events Discontinuations Selected laboratory analyses
Other Studies										
1001 Japanese Non-Comparative Deep-Seated Mycoses Study Japan	Jan. 1999/ ongoing	OL, MC, uncontrolled study of intravenous and oral voriconazole in the treatment of patients with deep-seated mycoses	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 3-4 mg/kg q 12 h → voriconazole PO 200-300 mg bid Voriconazole oral 300 mg bid x 2 doses on Day 1 → 200 mg bid Patients weighing less than 40 kg should have all doses of voriconazole reduced by half. Dose reduction permitted based on adverse events and plasma monitoring Total duration minimum of 3 days and maximum of 12 weeks	N/A		N/A	Not included		N/A	Serious adverse events

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
1010 Comparative Paracoccioides Study So. America	Oct. 2000/ ongoing	OL, MC, randomized, comparative study of voriconazole vs. itraconazole in the treatment of acute and chronic Paracoccidioidomycosis	Voriconazole PO 400 mg bid on Day 1 → 200 mg bid Patients weighing <40 kg should have all doses of voriconazole reduced by half. Itraconazole 100 mg PO bid Total duration minimum of 6 months and maximum of 12 months depending on global response at 6 months..	N/A		N/A	Not included		N/A	Serious adverse events

DB = double blind; ITT = Intention to Treat; MITT = Modified Intention to Treat; MC = multicenter; bid=twice daily; OL= open label; OLAT = Other Licensed Antifungal Therapy; N/A = not available; PO=orally; PP = Per Protocol; IV=intravenously
*Completed study on Initial Randomized Therapy (IRT)
#For ongoing studies, patients included in efficacy analysis are those who completed study by efficacy cut-off date of 20 Sep 1999.

APPENDIX 3. SUMMARIES OF SUPPORTIVE STUDIES

Chronic Fungal Infection Study (303)

The Chronic Fungal Infection Study (303) was one of the initial studies in the voriconazole clinical development program, designed to provide initial evidence of efficacy in a population of patients with chronic fungal infections and evaluate the tolerability in these patients. This study was conducted in Europe from July 1993 to December 1996. The objectives of the study were to assess the efficacy, safety and tolerability of oral voriconazole in the treatment of chronic invasive infections caused by *Aspergillus* spp. or *Candida* spp. and to determine the relationship between plasma concentrations of voriconazole and efficacy. Patients who were not severely neutropenic, with a diagnosis of invasive aspergillosis or invasive candidiasis, where the nature of the infection was indolent and not considered immediately life-threatening, were eligible for the study. Patients were treated with oral voriconazole 200 mg bid for a duration of four to 24 weeks. Following a planned interim analyses of results for the first evaluable patients, a protocol amendment allowed incremental dose escalation up to 350 mg bid.

The primary efficacy endpoint was clinical response as assessed by the investigator. Secondary efficacy variables included mycological response and survival. Efficacy analyses were performed on an Intention to Treat population (all patients who had received at least one dose of voriconazole) and a Per Protocol population (patients fulfilling major protocol entry criteria).

No formal sample size calculation was performed; a target of 50 patients was pre-planned in the protocol. Fifty-eight patients entered the study and are included in the Safety and Intention to Treat Populations. Twelve patients were excluded from the Per Protocol population, all because they took prohibited concomitant antifungal therapy; 46 patients are included in the Per Protocol population. Of the 58 patients who entered the study, 18 patients (31.0%) completed and 40 patients (69.0%) discontinued prematurely, primarily because of adverse events (seven patients), laboratory abnormalities (nine patients), death (six patients) and lack of efficacy (11 patients).

There were 41 males and 17 females; mean age was approximately 45 years and most patients were white. Sixty-seven percent of patients (39/58) had aspergillosis; most of these were pulmonary infections (n=29). Nineteen patients ((33%) had candidiasis; most of these were esophageal infections (n=13). The most common underlying diseases included acquired immunodeficiency syndrome (20/58, 35%), hematological or lymphoreticular malignancy (9/58, 16%), chronic obstructive pulmonary disease and other pulmonary conditions (8/58, 14%), and pulmonary tuberculosis (8/58, 14%).

Patients were treated with voriconazole for a median duration of 73 days (range 3 to 284 days). Seven patients had their dose escalated above 200 mg bid for either low plasma concentration (five patients) or failure (two patients). Doses in these patients included: 250 mg bid (five patients), 300 mg bid (one patient) and 400 mg bid (one patient)

Results of the clinical response at End of Therapy for the Intention to Treat and Per Protocol populations are shown in the Table A-1.

Table A-1 Chronic Fungal Infection Study (303) - Outcome at End of Therapy – Intention to Treat and Per Protocol Populations

Outcome		Intention to Treat Population (N=58) n (%)	Per Protocol Population (N=46) n (%)
Success	Complete	18 (31.0)	16 (34.8)
	Partial	17 (29.3)	17 (37.0)
	Total	35 (60.3)	33 (71.7)
Failure	Failure	16 (27.6)	11 (23.9)
	Not evaluable	7 (12.1)	2 (4.3)
	Total	23 (39.7)	13 (28.3)

Mycological response and survival are presented in Table A-2 and Table A-3.

Table A-2 Chronic Fungal Infection Study (303) – Mycological Response by Sponsor's Primary Diagnosis– Intention to Treat Population

Mycological Response	Aspergillosis (N=39) n (%)	Candidiasis (N=19) n (%)	Total (N=58) n (%)
Eradication	13 (33.3)	1 (5.3)	14 (24.1)
Not eradicated	1 (2.6)	4 (21.0)	5 (8.6)
Not evaluable	25 (64.1)	14 (73.7)	39 (67.2)
Total	39 (100.0)	19 (100.0)	58 (100.0)

Table A-3 Chronic Fungal Infection Study (303) – Survival – Intention to Treat Population

	Survival			
	Days from first dose			7 days after EOT
	30 n (%)	60 n (%)	90 n (%)	
Alive	50 (86.2%)	47 (81.0%)	42 (72.4%)	45 (77.6%)
Dead	6 (10.3%)	7 (12.1%)	11 (19.0%)	9 (15.5%)
Censored	2 (3.4%)	4 (6.9%)	5 (8.6%)	4 (6.9%)
Probability of survival	0.897	0.878	0.803	0.840
Approximate 95% CIl	0.818 – 0.975	0.793 – 0.963	0.698 – 0.908	0.744 – 0.936

CI = confidence interval; EOT = End of Therapy

The results of the plasma concentration analysis are included in the overall pharmacokinetic/pharmacodynamic analysis (Section 6) of this Briefing Document.

In this open label multi-center study, the efficacy, safety and tolerability of voriconazole was assessed in the treatment of chronic invasive aspergillosis and candidiasis. This was not a comparative study and therefore no hypothesis tests were performed. Success (complete or partial response) at End of Therapy was demonstrated in at least 60% of patients, with a similar rate of response for both aspergillosis and candidiasis patients in both the Intention to Treat and Per Protocol populations. Thirteen patients (22.4%) had eradication of aspergillosis on mycological assessment. The probability of survival at 90 days after initiation of voriconazole therapy was 80%. The results of this study performed early in the clinical program supported the continued evaluation of voriconazole in the treatment of patients with aspergillosis and candidiasis, at a dose of 200 mg bid.

Rare and Refractory Studies (309 and 604)

Studies 309 and 604 had identical objectives and designs. Study 309 was conducted in Europe and Australia from July 1998 to October 2000 and Study 604 was conducted in the U.S., Canada, and Thailand from December 1997 to June 2000. The efficacy results presented in this summary are an interim analysis done for submission in the November 2000 New Drug Application, on all patients entered into the study on or before 31 May 1999 (Study 309) or 26 May 1999 (Study 604). The results from these two studies are presented individually in the following sections. The primary objective of each study was to investigate the efficacy, safety and tolerability of voriconazole in the treatment of systemic and invasive fungal infections due to pathogens for which there is no licensed therapy; and in the treatment of systemic or invasive fungal infections in patients failing or intolerant of treatment with approved antifungal agents.

These were open label, non-comparative studies in which all patients received voriconazole, initiated as an intravenous loading dose of 6 mg/kg q 12 h for two doses or an oral loading dose of 400 mg bid for two doses, followed by maintenance dosing with 4 mg/kg q 12 h or 200 mg bid, respectively, for a total duration of 12 weeks. Eligible patients included patients who had been diagnosed with a systemic or invasive fungal infection for which there was no approved therapy and patients with a systemic or invasive fungal infection which was unsuccessfully treated or who had experienced intolerance or toxicity to an approved antifungal agent.

The primary endpoint was satisfactory global response at End of Therapy. A satisfactory global response was a ‘complete’ or ‘partial’ global response as assessed by the investigator. Time to death was a secondary endpoint. The only analysis population was the Modified Intention to Treat population, defined as patients who had received at least one dose of study drug and had a diagnosis of definite or probable fungal infection that was considered to be systemic or invasive at baseline as determined by the Sponsor.

Seventy four patients and 156 patients were entered into Studies 309 and 604, respectively. In Study 309, 37 patients were excluded from the Modified Intention to Treat analysis for the following reasons: no documented infections (n = 6), invalid specimens (n = 7) and entered after the cut-off date (n = 24). In Study 604, reasons for exclusion from the Modified Intention to Treat analysis in 45 patients included: no documented infections (n = 19) and entered after the cut-off date (n = 26). The disposition of patients as of the cut-off date of the interim analysis, is displayed in Table A-4.

Table A-4 Rare and Refractory Studies (309 and 604) – Patient Disposition – Safety Population¶

	Study 309 (N=74) n (%)	Study 604 (N=156) n (%)
Received Treatment	74 (100.0)	156 (100.0)
Completed the study	22 (29.7)	51 (32.7)
Discontinued the study	36 (48.6)	91 (58.3)
Discontinued due to AE	5 (6.8)	16 (10.3)
Discontinued due to laboratory abnormality	3 (4.1)	4 (2.6)
Death	11 (14.9)	37 (23.7)
Lack of efficacy	12 (16.2)	15 (9.6)
Other*	5 (6.8)	19 (12.2)
Ongoing on cutoff date	16 (21.6)	14 (9.0)

*Other for Study 309 includes protocol violations (n=2), lost to follow-up (n=2) and other miscellaneous reason (n=1). Other for Study 604 includes protocol violation (n=3), lost to follow-up (n=3), consent withdrawn (n=7), other miscellaneous reasons (n=6).
¶Per study summary page on case report form

There were 50 males and 24 females in Study 309 and 98 males and 58 females in Study 604. The mean age was approximately 43 years in both studies. In Study 309, 92% of patients were white; in Study 604, 72% of patients were white. Most patients had aspergillosis (37 patients in Study 309 and 70 patients in Study 604) or candidiasis (21 patients in Study 309 and 49 patients in Study 604). Table A-5 summarizes the categories of immunosuppression for patients in these studies.

Table A-5 Rare and Refractory Studies (309 and 604) - Categories of Immunosuppression – Safety Population

Category	Study 309 (N=74) n (%)	Study 604 (N=156) n (%)
Immunosuppression		
AIDS	16 (21.6)	31 (19.9)
Neutropenia	17 (23.0)	29 (18.6)
Other immunocompromised	27 (36.5)	72 (46.2)
Immunocompetent	14 (18.9)	24 (15.4)

Most patients had been treated with prior antifungal therapy with four weeks of starting the study (approximately 95%); the most frequently used prior antifungal therapy was amphotericin B (62% of patients in Study 309 and 78% of patients in Study 604).

The median total duration of voriconazole therapy, and durations of intravenous and oral therapy were 58 days, 12 days, and 65 days, respectively, for Study 309 and 56 days, 9 days, and 79 days, respectively, for Study 604.

Results of the primary efficacy analysis, global response for the Modified Intention to Treat population are shown in Table A-6.

Table A-6 Rare and Refractory Studies (309 and 604) - Global Response at End of Therapy - Modified Intention to Treat Population

Study Primary diagnosis	Global Response		
	Success n/N (%)	95% CI*	Failure n/N (%)
Study 309			
Aspergillosis	8/16 (50.0)	(24.7, 75.4)	8/16 (50.0)
Candidiasis	5/10 (50.0)	(18.7, 81.3)	5/10 (50.0)
Other**	6/11 (54.5)	(23.4, 83.3)	5/11 (45.5)
Total	19/37 (51.4)	(34.4, 68.1)	18/37 (48.6)
Study 604			
Aspergillosis	22/55 (40.0)	(27.0, 54.1)	33/55 (60.0)
Candidiasis#	19/32# (59.4)	(40.6, 76.3)	12/32# (37.5)
Other**	11/24 (45.8)	(25.6, 67.2)	13/24 (54.2)
Total#	52/111 (46.8)	(37.3, 56.6)	58/111 (52.3)

N = total number of patients in Modified Intention to Treat population with specific diagnosis
*95% CI = Exact 95% confidence interval for the proportion satisfactory.
** Other = all other classifications of primary diagnosis
Study 309 (N=11) Other includes scedosporiosis (n=3), cryptococcosis (n=2), fusariosis (n=1), chromoblastomycosis (n=1), *Mycoleptidiscus indicus* (n=1), *Trichophyton cutaneum* (n=1), mycetoma (n=1), mould unspecified (n=1).
Study 604 (N=24) Other includes cryptococcosis (n=8), scedosporiosis (n=3), fusariosis (n=4), *Paecilomyces* infection (n=2), Penicilliosis (n=1), histoplasmosis (n=1), coccidioidomycosis (n=1), *Exophiala jeanselmei* (n=1), *Blastomyces dermatiditis* (n=1), *Bipolaris* sp. (n=1), mixed fungal infection (n=1).
#One patient with candidiasis was lost to follow-up and as a result had no global response assessment performed at End of Therapy. This patient is included in the denominator of patients with candidiasis (n = 32) and the total (n=111), but not in either the Candidiasis success or failure categories (n=19, n=12, respectively) or the total success or failure categories.

Patient survival 90 days after the start of treatment is summarized in Table A-7.

Table A-7 Rare and Refractory Studies (309 and 604) - Patient Survival at 90 Days after Start of Therapy – Modified Intention to Treat Population

Study Primary Diagnosis	Survival at 90 Days after Start of Therapy	
	Proportion alive	95 % CI*
Study 309		
Aspergillosis	0.606	0.359 – 0.852
Candidiasis	0.788	0.525 – 1.000
Other**	0.727	0.464 – 0.990
Total	0.693	0.542 – 0.845
Study 604		
Aspergillosis	0.512	0.377 – 0.647
Candidiasis	0.674	0.505 – 0.842
Other**	0.831	0.680 – 0.982
Total	0.629	0.537 –0.721

*95% CI = 95% confidence interval for proportion alive
**Other = all other classifications of infections

Success at End of Therapy was demonstrated in 51.4% and 46.8% of the patients in the Modified Intention to Treat population, in Studies 309 and 604, respectively, including patients with invasive aspergillosis or serious *Candida* infections, all of whom had failed or were intolerant to approved therapy, and also including patients with invasive infections caused by other fungal pathogens. More than 60% of these patients were alive 90 days after starting therapy.

APPENDIX 4. POOLED ANALYSES

Voriconazole Efficacy Response Assessment Methodology

The procedures used to form a pooled database and perform a standardized efficacy assessment of patients treated with voriconazole for various fungal infections are referred to as the Voriconazole Efficacy Response Assessment (VERA). This pooled analysis was included for the NDA submission in Nov. 2000, and has not been updated with subsequently completed studies (including the Global Comparative Aspergillosis Study [307/602]). The VERA process was conducted in accordance with predefined operating procedures and the Sponsor evaluated individual patient data for key parameters using prespecified criteria. This central review enabled the correct allocation of fungal infections (species, site, and certainty of diagnosis) across protocols. For a patient to be included in the pooled analysis, at least one ”*definite*” or ”*probable*” fungal infection must have been present at baseline, with the exception of study 603 where both baseline and breakthrough infections were included. The definition of ‘*definite*’ or ‘*probable*’ infection was in accordance with the stipulations of the individual study protocol, where present.

Patients enrolled within comparative studies (305, 603 and interim data from 608), non-comparative studies (303, 304, 309, 604, and 1003) and newly-enrolled patients (i.e. patients that had not been enrolled in previous studies) in the compassionate program (301, 303A, 304A, 312, and 606) were analyzed for efficacy in accordance with the study-specific analyses described in the corresponding study reports. Eligibility for assessment was based on any voriconazole-treated patient being assessed once only at end of therapy in the first study the patient was enrolled, and, in ongoing studies, having been enrolled before the study-specific efficacy cut-off date for this submission. Empirically-treated patients in study 603 without invasive fungal infection were not eligible for VERA assessment. Patients who were enrolled in the extension studies (Studies 311 and 307) and patients who were enrolled in the compassionate program who had been previously enrolled in other studies were not included.

A total of 2138 patient identification numbers (PIDs) for patients treated with voriconazole (in 12 studies) and patients treated with comparator agents (in 3 comparative studies and in the historical control study 1003) were screened according to the criteria noted above. Some patients were entered into more than one study (i.e. Phase 2/3 study followed by treatment in extension protocols or compassionate program). Eligibility for VERA assessment was restricted to a single voriconazole treatment course per individual patient, i.e. from the first study in which voriconazole was administered. The patient identification numbers for the subsequent enrollment were excluded from the dataset of patients included in the pooled analysis. A total of 9 multiple PIDs were excluded from the VERA final population because of double enrollment. The result was a population of 736 voriconazole-treated patients on whom the pooled analyses were conducted, including patients treated for aspergillosis, esophageal candidiasis, serious *Candida* infections, and other fungal pathogens.

Table A-8 following table presents the derivation of voriconazole-treated patients included in the VERA analysis.

Table A-8 Derivation of the Efficacy Population for the Pooled Analyses

Study	Aspergillosis	Candidiasis	Esophageal Candidiasis	Rare	Mixed/multiple Infections	Total
301	61	9	3	30	6	109
303	25	5	11	0	0	41
303A	2	0	0	2	0	4
304	117	0	0	4	0	121
304A	15	0	0	3	0	18
305	0	0	191	0	0	191
309	14	3	6	9	5	37
312	3	0	0	0	2	5
603	6	11	0	4	0	21
604	54	22	9	23	3	111
606	25	6	4	9	5	49
608	0	29	0	0	0	29
Total	322	85	224	84	21	736

Each of the patients was reviewed for key elements including (i) primary underlying condition, (ii) hematological risk factor, (iii) previous antifungal treatment, (iv) infection details with pathogen, site and certainty of infection, and (v) outcome. The pooled efficacy analysis incorporated the assessments made by independent external experts or Data Review Committees where these were used for individual studies (Studies 304, 603 and 608). Where available, the Data Review Committee/external expert assessments took precedence over any other assessment. For those studies where an external expert or Data Review Committee was not employed, the sponsor-assessed outcome at End of Therapy used the investigator assessment, within the context of other available pertinent information. The sponsor was allowed only to downgrade and never upgrade an investigator outcome assessment. In randomized studies, both voriconazole and comparator-treated patients were assessed, and the assessors were blinded to the treatment allocation. The patients in the pooled analyses were classified by underlying risk factors to allow additional examination of the data. A patient with a complete or partial response was classified as a success and a patient with a response of stable, failure, or unevaluable, or with discontinuation due to intolerance or protocol reasons were classified as a failure. Discontinuation due to intolerance or protocol reasons included patients who discontinued study due to increased liver function tests or adverse events, even if the investigator's assessment of outcome at end of treatment was a success.

Pooled Analysis: Aspergillosis

The objective of the pooled analysis was the consistent assessment of certainty of diagnosis and outcome following voriconazole therapy in patients with invasive aspergillosis across studies. All patients were assessed according to the Voriconazole Efficacy Response Assessment and were included in the pooled analysis if they had a definite or probable infection and adequate information for evaluation (detailed methodology provided above). The Global Comparative Aspergillosis Study (307/602) was not included in the pooled population because it was not part of the original New Drug Application (NDA). The final report on Study 307/602 has been filed to the Food and Drug Administration and is reported as an individual study in the Briefing Document.

The pooled analysis allows examination of efficacy data among patients who received voriconazole as salvage therapy (following more than five days of prior systemic antifungal therapy), those with poor prognostic factors including allogeneic bone marrow transplantation, graft *vs*. host disease, as well as those with central nervous system aspergillosis.

Patient Disposition

Of the voriconazole patients screened for the pooled analysis, 322 were found to have a definite or probable *Aspergillus* infection only. Ten additional patients had aspergillosis as part of a mixed fungal infection. The numbers of voriconazole patients with aspergillosis from each of the studies is shown in Table A-9.

Table A-9 Aspergillosis Pooled Efficacy Analysis – Population

	Aspergillosis (N=322) n	Mixed Aspergillosis* (N=10) n	Total Aspergillosis** (N=332) n
Non-comparative Aspergillosis Study (304)	117	0	117
Other Clinical Studies			
Rare and Refractory Studies (309 and 604)	68	1	69
Chronic Fungal Infection Study (303)	25	0	25
Empirical Therapy Study (603)	6	0	6
Compassionate Use (301, 312, 606, 303A, 304A)	106	9	115

*Aspergillosis with mixed fungal infection
**All patients with *Aspergillus* infections, excluding Global Comparative Aspergillosis Study (307/602)

Baseline Characteristics/Demographics

Demographics for the aspergillosis pooled efficacy analysis population are summarized in Table A-10.

Table A-10 Aspergillosis Pooled Efficacy Analysis - Demographic Characteristics

Demographic Characteristics	Study 304** (N=117) n (%)	Other Clinical Studies (N=99) n (%)	Compassionate Use (N=106) n (%)	Mixed* (N=10) n (%)	Total# (N=332) n (%)
Gender					
Male	67 (57.3)	59 (59.6)	73 (68.9)	7 (70)	206 (62)
Female	50 (42.7)	40 (40.4)	33 (31.1)	3 (30)	126 (38)
Age (years)					
< 12	0	0	29 (27.4)	1 (10)	30 (9.0)
≥12, <45	50 (42.7)	45 (45.4)	42 (39.6)	6 (60)	143 (43.1)
≥45, <65	50 (42.7)	44 (44.4)	30 (28.3)	1 (10)	125 (37.7)
≥65	17 (14.6)	10 (10.1)	5 (4.7)	2 (20)	34 (10.2)
Mean	46.4	44.3	30.2	34.2	40.2
Race					
White	115 (98.3)	85 (85.9)	91 (85.8)	9 (90)	300 (90.4)
Black	1 (0.9)	5 (5.1)	5 (4.7)	0	11 (3.3)
Asian	0	1 (1.0)	6 (5.7)	0	7 (2.1)
Hispanic	0	4 (4.0)	0	1 (10)	5 (1.5)
Other	1 (0.9)	4 (4.0)	4 (3.8)	0	9 (2.7)

*Patients with aspergillosis as part of a mixed fungal infection
**Non-Comparative Aspergillosis Study (304)
All patients with *Aspergillus* infections, excluding Global Comparative Aspergillosis Study (307/602)

Patients less than 12 years of age were entered only in the compassionate use program.

Table A-11 provides a summary of primary treatment compared to salvage therapy, site of infection, underlying disease, hematologic risk factors and neutrophil count for the pooled aspergillosis population at baseline.

Table A-11 Aspergillosis Pooled Efficacy Analysis – Baseline Characteristics - Primary Compared to Salvage Therapy, Site of Infection, Underlying Disease, Hematologic Risk Factors, and Neutrophil Status at Baseline

Demographic Characteristics	Study 304** (N=117) n (%)	Other Clinical Studies (N=99) n (%)	Compassionate use (N=106) n (%)	Mixed* (N=10) n (%)	Total# (N=332) n (%)
Primary *vs.* Salvage					
Primary Therapy	53 (45.3)	25 (25.3)	6 (5.7)	0	84 (25.3)
Salvage Therapy	64 (54.7)	74 (74.7)	100 (94.3)	10 (100.0)	248 (74.7)
Site of Infection					
Pulmonary	81 (69.2)	52 (52.5)	44 (41.5)	7 (70.0)	184 (55.4)
Central Nervous System	19 (16.2)	9 (9.1)	17 (16.0)	0	45 (13.6)
Disseminated##	9 (7.7)	8 (8.1)	12 (11.3)	0	29 (8.7)
Sinus	5 (4.3)	12 (12.1)	15 (14.2)	1 (10.0)	33 (9.9)
Hepatic/Hepatosplenic	1 (0.9)	1 (1.0)	5 (4.7)	0	7 (2.1)
Bone	0	6 (6.1)	3 (2.8)	0	9 (2.7)
Skin/subcutaneous	0	8 (8.1)	3 (2.8)	0	11 (3.3)
Other¶	2 (1.7)	3 (3.0)	7 (6.6)	2 (20.0)	14 (4.2)
Underlying Disease				0	
Cancer	87 (74.4)	52 (52.5)	45 (42.5)	3 (30.0)	187 (56.3)
Hematologic Malignancy	79 (67.5)	45 (45.4)	40 (37.7)	3 (30.0)	167 (50.3)
Solid Organ Malignancy	8 (6.8)	7 (7.1)	5 (4.7)	0	20 (60.2)
Hematological condition (*e.g.*, CGD, aplastic anemia)	9 (7.7)	10 (10.1)	19 (17.9)	1 (10.0)	39 (11.7)
HIV/AIDS	5 (4.3)	9 (9.1)	9 (8.5)	1 (10.0)	24 (7.2)
Immunosuppression: drug or disease induced	7 (6.0)	4 (4.0)	11 (10.4)	1 (10.0)	23 (6.9)
Solid organ transplantation	6 (5.1)	7 (7.1)	8 (7.5)	2 (20.0)	23 (6.9)
Pulmonary disorder (*e.g.* COPD)	0	8 (8.1)	4 (3.8)	0	12 (3.6)
Injury, trauma, post-surgical	1 (0.9)	4 (4.0)	2 (1.9)	2 (20.0)	9 (2.7)
Hematologic Risk Factors					
BMT/PSCT (includes GvHD)	28 (23.9)	36 (36.4)	23 (21.7)	2 (20.0)	89 (26.8)
Relapsed hematologic malignancy	6 (5.1)	5 (5.1)	3 (2.8)	0	14 (4.2)
Prolonged neutropenia¶¶	0	18 (18.2)	12 (11.3)	1 (10.0)	31 (9.3)
None known	83 (70.9)	40 (40.4)	68 (64.2)	7 (70.0)	198 (59.6)
Neutrophil Status&					
ANC <500 cells/mm^3	23 (19.7)	12 (12.1)	2 (1.9)	0	37 (11.1)
ANC ≥500 cells/mm^3	66 (56.4)	64 (64.6)	6 (5.7)	1 (10.0)	137 (41.3)
Missing	28 (23.9)	23 (23.2)	98 (92.4)	9 (90.0)	158 (47.6)

AIDS=acquired immunodeficiency syndrome; ANC=absolute neutrophil count; BMT=bone marrow transplant; CGD=chronic granulomatous disease; COPD=chronic obstructive pulmonary disease; GvHD=graft *vs.* host disease; HIV=human immunodeficiency virus; PSCT=peripheral stem cell transplant
*Patients with aspergillosis as part of a mixed fungal infection, **Non-Comparative Aspergillosis Study (304)
All patients with *Aspergillus* infections, excluding Global Comparative Aspergillosis Study (307/602)
##Hierarchy for multiple infection sites: central nervous system (CNS) with/without other site classified as "CNS"; all other patients with more than one site classified as "disseminated".
¶Other includes temporomandibular joint (n=1), kidney (n=3), spinal cord (n=1), burn wound (n=2), intra-abdominal infection (n=3), subphrenic abscess (n=1), pleural (n=1), ascites/pleural fluid (n=1), tracheobronchial (n=1)
¶¶ Prolonged neutropenia – absolute neutrophil count < 500cells/mm^3 for greater than ten days prior to receiving voriconazole & Includes only patients who had neutrophil counts or white blood cell differential counts performed.

Of the 332 patients treated with voriconazole only; 25.3% received voriconazole as primary therapy and 74.7% received voriconazole as salvage therapy (prior systemic antifungal therapy active against *Aspergillus*, for more than five days). The proportion of patients receiving salvage therapy was highest in the compassionate use studies (94.3%).

Duration of therapy

Table A-12 Aspergillosis Pooled Efficacy Analysis – Duration of Therapy (Actual Time)

	Aspergillosis (N=322)	Mixed Aspergillosis* (N=10)	Total Aspergillosis** (N=332)
Median duration (days)#	62	12	61
Range (days)	1-977	1-381	1-977

*Aspergillosis with mixed fungal infection
** All patients with *Aspergillus* infections, excluding Global Comparative Aspergillosis Study (Study 307/602)
#Actual time

Efficacy

The overall outcome and the outcome by primary or salvage therapy (for which an outcome of unevaluable = failure) are shown in Table A-13 for the total population and by clinical trial compared with compassionate use patient outcomes.

Table A-13 Aspergillosis Pooled Efficacy Analysis – Overall Outcomes and Outcome by Primary or Salvage Therapy in the Total Population and by Clinical Trial Compared with Compassionate Use Patients

Demographic Characteristics	Study 304** n (%)	Other Clinical Studies n (%)	Compassionate use n (%)	Mixed* n (%)	Total# n (%)
Overall##	**(N=117)**	**(N=99)**	**(N=106)**	**(N=10)**	**(N=332)**
Success	56 (47.9)	43 (43.4)	41 (38.7)	4 (40.0)	144 (43.4)
Failure	61 (52.1)	56 (56.6)	65 (61.3)	6 (60.0)	188 (56.6)
Primary therapy	**(N=53)**	**(N=25)**	**(N=6)**	**(N=0)**	**(N=84)**
Success	28 (52.8)	12 (48.0)	4 (66.7)	0	44 (52.4)
Failure	25 (47.2)	13 (52.0)	2 (33.3)	0	40 (47.6)
Salvage therapy¶	**(N=64)**	**(N=74)**	**(N=100)**	**(N=10)**	**(N=248)**
Success	28 (43.8)	31 (41.9)	37 (37.0)	4 (40.0)	100 (40.3)
Failure	36 (56.3)	43 (58.1)	63 (63.0)	6 (60.0)	148 (59.7)

*Patients with aspergillosis as part of a mixed fungal infection
**Non-Comparative Aspergillosis Study (304)
All patients with *Aspergillus* infections, excluding Global Comparative Aspergillosis Study (307/602)
##Success = complete or partial response; Failure = stable, failure, unevaluable or discontinued for therapy intolerance or other reasons
¶Salvage therapy => five days of previous systemic antifungal therapy

The overall success rate was highest in Non-Comparative Aspergillosis Study (304, 47.9%), followed by the other clinical studies (43.4%), and then compassionate use (38.7%).

For the 84 patients receiving voriconazole as primary therapy, the success rate of 52.4% in the pooled population was similar to that for the 53 patients in the Non-Comparative

Aspergillosis Study (304) who received voriconazole as primary therapy and qualified for the pooled analysis (52.8%). The success rate was 66.7% for patients who received voriconazole as primary therapy in the compassionate use program. In the pooled voriconazole population, success following voriconazole therapy was seen in 40.3% of patients who received voriconazole as salvage therapy. This is similar to the 43.8% success seen among salvage patients in the Non-Comparative Aspergillosis Study (304). Ten additional patients had infections due to multiple fungal pathogens including *Aspergillus* species and were treated with voriconazole as salvage therapy. Among these ten patients, four had successful outcomes.

Outcome by Primary Underlying Condition

In the pooled database, 187/332 patients (56.3%) treated with voriconazole had cancer reported as the primary underlying condition. The overall success rate in treatment of *Aspergillus* infection in these cancer patients was 44.4%. Table A-14 shows success according to underlying disease.

Table A-14 Aspergillosis Pooled Efficacy Analysis – Successful Outcome by Underlying Disease in the Total Population and by Clinical Trial Compared with Compassionate Use

Underlying Disease	Study 304** (N=117)	Other Clinical Studies (N=99)	Compassionate use (N=106)	Mixed* (N=10)	Total# (N=332)
	Success n/N (%) of patients				
Cancer	46/87 (52.9)	22/52 (42.3)	14/45 (31.1)	1/3	83/187 (44.4)
Hematological condition (e.g. CGD, aplastic anemia)	3/9 (33.3)	3/10 (30.0)	9/19 (47.4)	1/1	16/39 (41.0)
AIDS and HIV	1/5 (20.0)	5/9 (55.6)	1/9 (11.1)	0/1	7/24 (29.2)
Immuno-suppression	2/7 (28.6)	2/4 (50.0)	3/11 (27.3)	0/1	7/23 (30.4)
Post solid organ transplant	3/6 (50.0)	4/7 (57.1)	3/8 (37.5)	2/2	12/23 (52..2)
Pulmonary disorders	0/0	3/8 (37.5)	3/4 (75.0)	0	6/12 (50.0)
Injury, trauma, post surgical	0/1	0/0	2/2 (100.0)	0/2	3/9 (33.3)

AIDS = acquired immunodeficiency syndrome; CGD = chronic granulomatous disease; HIV = human immunodeficiency virus
*Patients with aspergillosis as part of a mixed infection
**Non-Comparative Aspergillosis Study (304)
All patients with *Aspergillus* infections, excluding Global Comparative Aspergillosis Study (307/602)

Outcome by Hematological Risk Factors

Among the 75 voriconazole patients who had allogeneic bone marrow transplants (BMT), 20 patients (26.7%) had successful outcomes while 14/50 patients (28.0%) with graft *vs.* host disease and 6/14 patients (42.9%) with relapsed hematological malignancy also had successful outcomes following voriconazole therapy.

Outcome by Site of Infection

Table A-15 provides a summary of successful outcomes of patients with *Aspergillus* infections at various sites.

Table A-15 Aspergillosis Pooled Efficacy Analysis - Outcomes by Site of Infection

Site	Aspergillosis (N=322)	Mixed Aspergillosis* (N=10)	Total Aspergillosis** (N=332)
	Success n/N (%)		
Central nervous system	11/45 (24.4)	0	11/45 (24.4)
Disseminated#	16/29 (55.2)	0	16/29 (55.2)
Pulmonary	85/177 (48.0)	3/7	88/184 (47.8)
Sinus	11/32 (34.4)	1/1	12/33 (36.4)
Skin/subcutaneous	6/11 (54.5)	0	6/11 (54.5)
Bone	4/9 (44.4)	0	4/9 (44.4)
Hepatic/Hepatosplenic	3/7 (42.9)	0	3/7 (42.9)
Other	4/12 (33.3)	0/2	4/14 (28.6)
Total	140/322 (43.5)	4/10	148/332 (44.6)

*Aspergillosis as part of a mixed fungal infection
** All patients with *Aspergillus* infections, excluding Global Comparative Aspergillosis Study (307/602)
#Hierarchy for multiple infection sites: central nervous system with/without other site classified as "CNS"; all other patients with more than one site classified as "disseminated".

Patients treated with voriconazole who had disseminated, pulmonary, hepatic/hepatosplenic, bone, and skin/subcutaneous involvement and were included in the pooled database had success rates ranging from 42.9% to 55.2%, while those with aspergillosis involving the central nervous system and sinuses had success rates of 24.4% and 36.4%, respectively. Among the 11 patients with successful outcomes following therapy with voriconazole for central nervous system (CNS) aspergillosis, nine survived for over 90 days (Table A-15).

Table A-16 shows the long-term outcome of patients with central nervous system (CNS) aspergillosis who had success following voriconazole therapy.

Table A-16 Aspergillosis Pooled Efficacy Analysis - Outcome of Patients with Central Nervous System (CNS) Aspergillosis Successfully Treated with Voriconazole

Patient	Underlying condition	Duration of voriconazole therapy (days)	Final outcome
304-172	Liver transplant	32	Died due to concurrent illness (Day 78). Partial response
304-842	Lymphoma	60	Died due to study-emergent illness (day 78). Partial response
304-567	Allogeneic BMT	96	Survived – Day 218 (Last patient visit)
301-001	Post-mastoidectomy	100	Survived (complete response at End of Therapy)
604-6002	Hematological malignancy	154	Survived (partial response at End of Therapy)
304-182	Hematological malignancy	174	Died due to concurrent illness (Day 175). Partial response
303A-115	Chronic granulomatous disease	222	Survived (partial response at End of Therapy)
301-001	Systemic lupus erythematosus, autoimmune hemolytic anemia	230	Survived (complete response at End of Therapy)
606-15	Wiscott Aldrich syndrome, status post BMT x 2	368	Therapy ongoing (20 September 1999). Partial response
304A-001	Hematological malignancy	418	Died due to concurrent illness (Day 420). Partial response
301-001	None known – infant with probable immunodeficiency	800	Therapy ongoing (20 September 1999)

BMT = bone marrow transplant

Conclusions

The pooled analysis provided summary efficacy information on a total of 322 patients with confirmed *Aspergillus* infections and an additional ten patients with confirmed *Aspergillus* infections as part of a mixed infection. In the 332 patients with confirmed *Aspergillus* infections, over half had success following primary therapy with voriconazole and 40.3% had success following voriconazole as salvage therapy. These patients had risk factors for poor prognosis, including acute leukemia, bone marrow transplant (BMT), neutropenia, graft *vs.* host disease and central nervous system (CNS) infections. Forty-five of these patients had central nervous system involvement and 11 (24.4%) had successful outcomes.

Pooled Analysis: Fungal Infections due to Emerging Pathogens

The objective of the pooled analysis was the consistent assessment of certainty of diagnosis and outcome following voriconazole therapy for rare and refractory fungal infections across studies. All patients were assessed according to the Voriconazole Efficacy Response Assessment and were included in the pooled analysis if they had a definite or probable infection and adequate information for evaluation (detailed methodology provided above).

In the pooled analysis, salvage patients were classified as efficacy failures (refractory) or intolerant of prior antifungal therapy. Refractory infection or "efficacy failure" was defined as failure to respond to a previous systemic antifungal at a therapeutic dose. This applied only to patients who received voriconazole as salvage therapy, defined as "that following more than five days of treatment with a previous systemic antifungal agent, at therapeutic doses, for the same episode of infection, with a suggested gap of no more than five days between stopping the last antifungal and the start of voriconazole.

The numbers of patients treated as primary or salvage therapy are summarized in Table A-17.

Table A-17 Rare and Refractory Pooled Efficacy Analysis – Disposition by Primary or Salvage Therapy Use

Study Medication Use	*Fusarium* infections (N = 11)	*Scedosporium* infections (N = 32)	Other fungal infections (N = 41)	Mixed* (N = 17)	Total infections** (N = 101)
Primary therapy	1	3	10	2	16
Salvage therapy-efficacy and intolerance	0	0	4	4	8
Salvage therapy-efficacy failure	9	22	25	10	66
Salvage therapy-intolerance	1	1	1	0	3
Salvage therapy-unknown	0	6	1	1	8
Total	11	32	41	17	101

*Seventeen patients with mixed site or multiple site fungal infections: two from Study 604, five from Study 309 and ten from the compassionate use studies
**Total: Patients with rare and refractory infections alone or as part of a mixed fungal infection

The majority of patients received voriconazole as salvage therapy. Of these 85 patients, most (66 of 85, 78%) were refractory to prior therapy and eight were both refractory to and intolerant of prior antifungal therapy.

Patient disposition

There were 84 patients who had fungal infections caused by more unusual fungal pathogens (non-*Aspergillus*, non-*Candida*) in the pooled population. An additional 17 patients had rare or refractory fungal infections as part of a mixed fungal infection. The numbers of voriconazole patients with rare and refractory fungal infections (with *Scedosporium* and *Fusarium* infections listed separately as well) from each of the studies is shown in Table A-18.

Table A-18 Rare and Refractory Pooled Efficacy Analysis - Population

Studies	Rare and/or refractory (only) (N=84)	Rare and/or refractory (mixed)* (N=17)	Total** (N=101)
Other Clinical Studies			
Non-Comparative Aspergillosis Study (304)			
Total rare and refractory infections	4	0	4
Scedosporium infections	2	0	2
Fusarium infections	1	0	1
Rare and Refractory Studies (309 and 604)			
Total rare and refractory infections	32	7	39
Scedosporium infections	5	0	5
Fusarium infections	4	2	6
Empirical Therapy Study (603)			
Total rare and refractory infections	4	0	4
Scedosporium infections	0	0	0
Fusarium infections	0	0	0
Compassionate Use (301, 312, 606, 303A, 304A)			
Total rare and refractory infections	44	10	54
Scedosporium infections	25	3	28
Fusarium infections	6	2	8
Total			
Total Rare and Refractory infections	84	17	101
Scedosporium infections	32	3	35
Fusarium infections	11	4	15

*Seventeen patients with mixed fungal infection: two from Study 604, five from Study 309 and ten from the compassionate use studies
**Total: patients with rare and refractory infections alone or as part of a mixed fungal infection

Baseline Characteristics/Demographics – *Scedosporium* and *Fusarium*

Table A-19 summarizes demography for patients with *Scedosporium* infections.

Table A-19 Rare and Refractory Pooled Efficacy Analysis - *Scedosporium* Infections - Demographic Characteristics

Demographic Characteristics	*Scedosporium* (alone) (N=32) n (%)	*Scedosporium* (mixed)* (N=3) n (%)	*Scedosporium* (total)** (N=35) n (%)
Gender			
Male	16 (50.0)	1 (33.3)	17 (48.6)
Female	16 (50.0)	2 (66.7)	18 (51.4)
Age (years)			
< 12	3 (9.4)	1 (33.3)	4 (11.4)
≥12, <45	14 (43.8)	2 (66.7)	16 (45.7)
≥45, <65	14 (43.8)	0	14 (40.0)
≥65	1 (3.1)	0	1 (2.9)
Mean (years)	39.0	12.3	36.7
Race			
White	31 (96.9)	2 (66.7)	33 (94.3)
Black	0	0	0
Asian	0	0	0
Hispanic	0	0	0
Other	1 (3.1)	1 (33.3)	2 (5.7)

*Patients with *Scedosporium* as part of a mixed infection
**All patients with *Scedosporium* infections

Table A-20 provides a summary of primary compared to salvage therapy, site of infection, underlying disease, hematologic risk factors and neutrophil count for the pooled *Scedosporium* population at baseline.

Table A-20 Rare and Refractory Pooled Efficacy Analysis – *Scedosporium* Infections - Primary Compared to Salvage Therapy, Site of Infection, Underlying Disease, Hematologic Risk Factor, Neutrophil Status at Baseline

	***Scedosporium* (alone) (N=32) n (%)**	***Scedosporium* (mixed)* (N=3) n (%)**	**Scedosporium (total)** (N=35) n (%)**
Primary *vs.* Salvage Therapy			
Primary therapy	3 (9.4)	0	3 (8.6)
Salvage therapy	29 (90.6)	3 (100.0)	32 (91.4)
Site of Infection			
Central nervous system	13 (40.6)	0	13 (37.1)
Disseminated#	5 (15.6)	2 (66.7)	7 (20.0)
Other##	14 (43.8)	1 (33.3)	15 (42.9)
Underlying Disease			
Cancer	15 (46.9)	3 (100.0)	18 (51.4)
Hematologic Malignancy	12 (37.5)	3 (100.0)	15 (42.9)
Solid Organ Malignancy	3 (9.4)	0	3 (8.6)
Hematological condition (e.g., CGD, Aplastic anemia)	2 (6.3)	0	2 (5.7)
Immunosuppression: drug or disease induced	6 (18.8)	0	6 (17.1)
Solid organ transplant	3 (9.4)	0	3 (8.6)
Injury, trauma, post-surgical	5 (15.6)	0	5 (14.3)
Other disorder	1 (3.1)	0	1 (2.9)
Hematologic Risk Factors			
BMT/PSCT (includes GvHD)	3 (9.4)	1 (33.3)	4 (11.4)
Prolonged neutropenia¶	3 (9.4)	1 (33.3)	4 (11.4)
None known	26 (81.3)	1 (33.3)	27 (77.1)
Neutrophil Status¶¶			
ANC <500 cells/mm^3	3 (9.4)	0	3 (8.6)
ANC ≥ 500 cells/mm^3	4 (12.5)	0	4 (11.4)
Missing	25 (78.1)	3 (100.0)	28 (80.0)

ANC = absolute neutrophil count; BMT = bone marrow transplant; CGD = chronic granulomatous disease; GvHD = graft *vs*. host disease; PSCT = peripheral stem cell transplant
*Patients with *Scedosporium* as part of a mixed infection
**All patients with *Scedosporium* infections
#Hierarchy for multiple infection sites: central nervous system (CNS) with/without other site classified as "CNS"; all other patients with more than one site classified as "disseminated".
##Other includes pulmonary (n = 8), skin (n = 2), blood (n = 1), bone/joint (n = 4)
¶Prolonged neutropenia – absolute neutrophil count < 500 cells/mm^3 for greater than 10 days prior to receiving voriconazole
¶¶Includes only patients who had neutrophil counts or white blood cell differential counts performed.

Table A-21 Rare and Refractory Pooled Efficacy Analysis - *Fusarium* Infections - Demographic Characteristics

Demographic Characteristics	*Fusarium* (alone) (N=11) n	*Fusarium* (mixed)* (N=4) n	*Fusarium* (total)** (N=15) n (%)
Gender			
Male	9	3	12 (80.0)
Female	2	1	3 (20.0)
Age (years)			
<12	2	0	2 (13.3)
≥12, <45	2	2	4 (26.7)
≥45, <65	5	2	7 (46.7)
≥65	2	0	2 (13.3)
Mean	45.1	38	43.2
Race			
White	11	1	12 (80.0)
Black	0	1	1 (6.7)
Asian	0	0	0
Hispanic	0	1	1 (6.7)
Other	0	1	1 (6.7)

**Fusarium* as part of a mixed infection
**All patients with *Fusarium* infections

Table A-22 provides a summary of primary compared to salvage therapy, site of infection, underlying disease, hematologic risk factors and neutrophil count for the pooled *Fusarium* population at baseline.

Table A-22 Rare and Refractory Pooled Efficacy Analysis – *Fusarium* Infections - Primary Compared to Salvage Therapy, Site of Infection, Underlying Disease, Hematologic Risk Factor, Neutrophil Status at Baseline

	***Fusarium* (alone) (N=11) n (%)**	***Fusarium* (mixed)* (N=4) n (%)**	***Fusarium* (total)** (N=15) n (%)**
Primary *vs.* Salvage Therapy			
Primary therapy	1 (9.1)	1 (25.0)	2 (13.3)
Salvage therapy	10 (90.9)	3 (75.0)	13 (86.7)
Site of Infection			
Eye	4 (36.4)	0	4 (26.7)
Disseminated***	5 (45.5)	1 (25.0)	6 (40.0)
Sinus	1 (9.1)	2 (50.0)	3 (33.3)
Skin	1 (9.1)	1 (25.0)	2 (13.3)
Underlying Disease			
Cancer	6 (54.5)	2 (50.0)	8 (53.3)
Hematologic Malignancy	5 (45.5)	2 (20)	7 (46.7)
Solid Organ Malignancy	1 (9.1)	0	1 (66.7)
Hematological condition (*e.g.*, CGD, aplastic anemia)	1 (9.0)	0	1 (6.7)
Immunosuppression: drug or disease induced	2 (18.2)	1 (25.0)	3 (20.0)
Injury, trauma, post-surgical	2 (18.2)	0	2 (13.3)
Hepatitis B	0	1 (25.0)	1 (6.7)
Hematologic Risk Factors			
Prolonged neutropenia¶	3 (9.1)	1 (25.0)	4 (26.7)
None known	8 (72.7)	3 (75.0)	11 (73.3)
Neutrophil Status#			
ANC <500 cells/mm^3	1 (9.1)	0	1 (6.7)
ANC $\geq$500 cells/mm^3	2 (18.2)	2 (50.0)	4 (26.7)
Missing	8 (72.7)	2 (50.0)	10 (66.7)

ANC = absolute neutrophil count; CGD = chronic granulomatous disease
*Patients with *Fusarium* as part of a mixed infection
**All patients with *Fusarium* infections
***Disseminated – greater than one noncontiguous site
¶Prolonged neutropenia = absolute neutrophil count < 500 cells/mm^3 for greater than 10 days prior to receiving voriconazole
#Includes only patients who had neutrophil counts or white blood cell differential counts performed.

Duration of Therapy

Table A-23, Table A-24, and Table A-25 present the duration of voriconazole in patients with infections due to rare fungal pathogens, infections due to *Scedosporium*, and infections due to *Fusarium*.

Table A-23 Rare and Refractory Pooled Efficacy Analysis – Duration of Therapy (Actual Time)

	Infections due to Rare Fungal Pathogens (N = 84)	**Mixed Rare Infections* (N = 17)**	**Total Rare Infections** (N = 101)**
Median Duration (Days)#	86	27	83
Range (Days)	1-1014	1-381	1-1014

*Patients with rare infection as part of a mixed infection
**All patients with rare infections
#Actual time

Table A-24 Rare and Refractory Pooled Efficacy Analysis – *Scedosporium* Infections - Duration of Therapy (Actual Time)

	***Scedosporium* Infections (N = 32)**	**Mixed *Scedosporium* Infections* (N = 3)**	**Total *Scedosporium* Infections** (N = 35)**
Median duration (days)#	130	27	123
Range (days)	1-1014	1-210	1-1014

*Patients with *Scedosporium* as part of a mixed infection
**All patients with *Scedosporium* infections
#Actual time

Table A-25 Rare and Refractory Pooled Efficacy Analysis – *Fusarium* Infections - Duration of Therapy (Actual Time)

	***Fusarium* Infections (N = 11)**	**Mixed *Fusarium* Infections* (N = 4)**	**Total *Fusarium* Infections** (N = 15)**
Median duration (days)#	57	26	49
Range (days)	11-401	24-101	11-401

*Patients with *Fusarium* as part of a mixed infection
**All patients with *Fusarium* infections
#Actual time

Efficacy

Outcome of voriconazole treatment by pathogen and by primary compared to salvage therapy is presented in Table A-26.

Table A-26 Rare and Refractory Pooled Efficacy Analysis - Analysis of Outcome by Organism

Pathogen	Patients with Rare Pathogens (N=84)		Patients with Rare Pathogens as Part of a Mixed Fungal Infection (N=17)		Total Patients with Rare Pathogens* (N=101)
	Success with primary therapy	Success with salvage therapy	Success with primary therapy	Success with salvage therapy	Success with primary or salvage Therapy
	Success n/N				
*Scedosporium apiospermum***	1/1	14/25	0	1/1	16/27
Scedosporium prolificans#	0/2	2/4	0	0/2	2/8
Fusarium sp.	0	2/7	0	1/2	3/9
Fusarium solani	0/1	2/3	1/1	0/1	3/6

*Total: patients with rare and refractory infections alone or as part of a mixed fungal infection: number of patients less than number of isolates as each patient could have more than one species isolated
**Includes *P. boydii*
#Includes *S. inflatum*

Of the 101 patients, 16 received voriconazole as primary treatment and 85 as salvage therapy (prior antifungal treatment for more than five days).

Outcome for *Scedosporium* infections

Successful outcomes were observed in 18 of 35 patients (51.4%) with *Scedosporium* infections. The majority of patients (32/35 [91.4%]) received voriconazole as salvage therapy.

The most common underlying condition in patients with *Scedosporium* infections was cancer, particularly hematologic malignancy. Six of 18 patients with cancer and four of 12 patients with hematologic malignancy who received voriconazole therapy had successful outcomes.

Successful outcome by site of infection for patients with *Scedosporium* infection only, as well as part of mixed fungal infections, is shown in Table A-27.

Table A-27 Rare and Refractory Pooled Efficacy Analysis - *Scedosporium* infections – Outcomes by Site of Infection

Site	*S. apiospermum* (N = 27)	*S. prolificans* (N = 8)
	Success n/N (%)	
Central nervous system*	7/11	0/2
Pulmonary	5/7	0/1
Cutaneous	0/2	-
Bone/joint	1/3	1/1
Disseminated	3/4	1/3
Blood	0	0/1
Total**	16/27(59.3)	2/8

CNS = central nervous system
*In four cases multiple sites were involved; Hierarchy for multiple infection sites: cerebral with/without other site classified as "cerebral"; all other patients with more than one site classified as "disseminated".
**Includes 32 patients with *Scedosporium* infections only and three patients with *Scedosporium* as part of a mixed infection
S. apiospermum includes *P. boydii; S. prolificans* includes *S. inflatum*

Table A-27 includes 32 patients with *Scedosporium* infections plus three patients with mixed infections for a total of 35 patients with *Scedosporium* infections. Of these 35 patients, 27 patients had infections with *S. apiospermum*, and 16 were successfully treated with voriconazole (59.3%). Two of eight patients (25%) with *S. prolificans* infection had successful outcomes.

Table A-28 includes the 13 patients with *Scedosporium* infection involving the central nervous system (CNS).

Table A-28 Rare and Refractory Pooled Efficacy Analysis - *Scedosporium* infections – Outcomes in Central Nervous System Infections

Patient number	Underlying Condition	Pathogen	Duration of Treatment (Days)	Final Outcome
50310019	End stage renal disease, cadaveric renal transplant, graft rejection	*P. boydii*	359*	Success (complete response)
03030001	Pilonidal cyst surgery	*P. boydii*	366	Success (partial response)
03130001	Near-drowning	*P. boydii*	450	Success (complete response)
50800025	Intravenous drug use, meningitis, encephalitis	*P. boydii*	209	Success (partial)
04050001	Near-drowning	*S. apiospermum*	419	Success (partial response)
04340001	Autoimmune glandular syndrome type II, incl. Autoimmune hepatitis, anti-smooth muscle Antibodies	*S. apiospermum*	361*	Success (partial response)
20390001	Non-insulin dependent diabetes mellitus	*S. apiospermum*	188*	Success (partial response)
04170001	Renal failure, vasculitis	*S. apiospermum*	115	Failure (investigator-assessed as partial response, died from cerebral hemorrhage Day 116)
04630001	Rheumatoid arthritis	*P. boydii*	4	Failure, D/C for septic shock Day four death four days later
10056037	Antiphospholipid syndrome, pulmonary embolism, lymphoma, splenectomy	*S. apiospermum*	114	Failure
01760001	Renal transplant	*S. apiospermum*	98	Failure
02920001	Non-Hodgkin lymphoma	*S.inflatum* (*S. prolificans*)	8	Failure, D/C for insufficient clinical response, died six days after D/C of voriconazole
03570001	Acute myelogenous leukemia	*S. prolificans*	31	Failure (withdrawn for relapsed AML)

*Voriconazole therapy ongoing at time of November 2000 NDA submission
D/C = discontinued

Outcome for *Fusarium* infections

Successful outcomes were observed in six of 15 patients (40.0%) with *Fusarium* infections. The majority of patients (13 of 15) received voriconazole as salvage therapy. The most common underlying condition among patients with *Fusarium* infections was cancer, particularly hematologic malignancy. Successful outcome was seen following voriconazole therapy in three of eight patients with cancer.

Table A-29 shows successful outcome by site of infection for patients with *Fusarium* infection, including those with *Fusarium* as part of mixed fungal infections.

Table A-29 Rare and Refractory Pooled Efficacy Analysis - *Fusarium* infections – Outcomes by Site of Infection

Site	Success n/N (%)
Eye	2/4
Sinus	2/3
Skin	1/2
Disseminated**	1/6
Total*	6/15 (40)

*Includes 11 patients with *Fusarium* infections only and four patients with *Fusarium* as part of a mixed infection
**Patients with *Fusarium* infections in more than one noncontiguous site classified as "disseminated".

For *Fusarium* infections there were four mixed fungal infections that included *Fusarium* spp., two involving one site and two involving multiple sites. Thus 15 patients had *Fusarium* infections. Six of these 15 patients (40%) were successfully treated with voriconazole.

Conclusions

Among patients with *Scedosporium* infections in the pooled analysis, successful outcomes were observed in 16 of 27 patients (59.3%), with infections due to *Scedosporium apiospermum* and two of eight patients with infections due to *Scedosporium prolificans.* Of these, 13 patients had documented central nervous system infections, seven of whom had successful outcomes following voriconazole therapy.

Among patients with *Fusarium* infections in the pooled analysis, six of 15 patients (40.0%) had successful outcomes, including patients with eye, sinus, and disseminated infections.

Pooled Analysis: Serious Systemic *Candida* Infections

The objective of the pooled analysis was the consistent assessment of certainty of diagnosis and outcome following voriconazole therapy for serious systemic *Candida* infections across studies. All patients were assessed according to the Voriconazole Efficacy Response Assessment and were included in the pooled analysis if they had a definite or probable infection and adequate information for evaluation (detailed methodology provided above).

Patient disposition

Of the 112 voriconazole treated patients screened for the pooled analysis, 88 had a definite or probable serious systemic *Candida* infection. In addition, three patients from the Rare and Refractory Studies (309/604) with definite or probable *Candida* infection who did not meet the protocol modified intention to treat criteria were excluded from the pooled analysis, resulting in a total population of 85 cases. These 85 voriconazole patients include eleven patients from Empirical Therapy Study (603) who developed serious systemic *Candida* infections in the setting of persistent fever and neutropenia.

An additional six patients had infections due to multiple fungal pathogens, including *Candida*, at one or multiple sites, for a total of 91 voriconazole-treated patients with serious systemic *Candida* infections.

Table A-30 presents disposition of patients with serious systemic *Candida* infections.

Table A-30 Serious Systemic *Candida* Pooled Efficacy Analysis - Population

	Candida **(alone) (N=85) n**	***Candida*** **(mixed)* (N=6) n**	***Candida*** **(total)** (N=91) n**
Clinical Trials	70	3	73
Compassionate use studies	15	3	18
Total	85	6	91

*Patients with *Candida* as part of a mixed infection
**All patients with *Candida* infections

Baseline Characteristics/Demographics

Demographic characteristics of patients with serious systemic *Candida* infection are presented in Table A-31.

Table A-31 Serious Systemic *Candida* Pooled Efficacy Analysis - Demographic Characteristics

Demographic Characteristics	**Clinical studies (N=70) n (%)**	**Compassionate use (N=15) n (%)**	**Mixed* (N=6) n (%)**	**Total** (N=91) n (%)**
Gender				
Male	43 (61.4)	11 (73.3)	2 (33.3)	56 (61.5)
Female	27 (38.6)	4 (26.7)	4 (66.7)	35 (38.5)
Age (years)				
< 12	0	3 (20.0)	0	3 (3.3)
≥12, <45	25 (35.7)	6 (40.0)	2 (33.3)	33 (36.3)
≥45, <65	30 (42.9)	4 (26.7)	2 (33.3)	36 (39.6)
≥65	15 (21.4)	2 (13.3)	2 (33.3)	19 (20.9)
Mean	46.8	32.7	52.8	47.2
Race				
White	57 (81.4)	13 (86.7)	5 (83.3)	75 (82.4)
Black	9 (12.9)	1 (6.7)	0	10 (11.0)
Asian	1 (1.4)	0	0	1 (1.1)
Hispanic	2 (2.9)	0	1 (16.7)	3 (3.3)
Other	1 (1.4)	1 (6.7)	0	2 (2.2)

*Patients with *Candida* infections as part of a mixed infection
**All patients with serious systemic *Candida* infections

Table A-32 provides a summary of site of infection, underlying disease, hematologic risk factors and neutrophil count for the pooled Systemic *Candida* population at baseline.

Table A-32 Serious Systemic *Candida* Pooled Efficacy Analysis –Site of Infection, Underlying Disease, Hematologic Risk Factor, Neutrophil Status at Baseline

	Clinical studies (N=70) n (%)	Compassionate use (N=15) n (%)	Mixed* (N=6) n (%)	Total** (N=91) n (%)
Site of Infection				
Blood	47 (67.1)	5 (33.3)	1 (16.7)	53 (58.2)
Disseminated#	10 (14.3)	7 (46.7)	2 (33.3)	19 (20.9)
Other##	13 (18.6)	3 (20.0)	3 (50.0)	19 (20.9)
Underlying Disease				
Cancer	30 (42.9)	8 (53.3)	2 (33.3)	40 (44.0)
Hematologic Malignancy	25 (35.7)	7 (46.7)	2 (33.3)	34 (37.4)
Solid Organ Malignancy	5 (7.1)	1 (6.6)	0	6 (6.6)
Hematological condition (*e.g.*, CGD, aplastic anemia)	2 (2.9)	3 (20.0)	0	5 (5.5)
HIV/AIDS	1 (1.4)	0	0	1 (1.1)
Immunosuppression: drug or disease induced	1 (1.4)	0	3 (50.0)	4 (4.4)
Solid organ transplantation	6 (8.6)	1 (6.7)	1 (16.7)	8 (8.8)
Pulmonary disorder (*e.g.* COPD)	7 (10.0)	0	0	7 (7.7)
Injury, trauma, post-surgical	12 (17.1)	1 (6.7)	0	13 (14.3)
Other disorder	11 (15.7)	1 (6.7)	0	12 (13.2)
Not specified	0	1 (6.7)	0	1 (1.1)
Hematologic Risk Factors				
BMT/PSCT (includes GvHD)	7 (10.0)	4 (26.7)	2 (33.3)	13 (14.3)
Relapsed hematologic malignancy	4 (5.7)	0	0	4 (4.4)
Prolonged neutropenia¶	14 (20.0)	3 (20.0)	0	17 (18.7)
None known	45 (64.3)	8 (53.3)	4 (66.7)	57 (62.6)
Neutrophil Status¶¶				
ANC <500 cells/mm^3	11 (15.7)	0	0	22 (24.2)
ANC ≥500 cells/mm^3	47 (67.1)	0	3 (50.0)	48 (52.7)
Missing	12 (17.1)	15 (100.0)	3 (50.0)	21 (23.1)

AIDS = acquired immunodeficiency syndrome; ANC = absolute neutrophil count; BMT = bone marrow transplant; CGD = chronic granulomatous disease; COPD = chronic obstructive pulmonary disease; GvHD = graft vs. host disease; HIV = human immunodeficiency virus; PSCT = peripheral stem cell transplant
*Patients with *Candida* as part of a mixed infection
**Total number of patients with serious systemic *Candida* infections
#Disseminated: biopsy-proven skin lesions, hepatosplenic, endophthalmitis, central nervous system, multiple sites (excluding esophagus, oropharynx, urine/bladder)
##Other includes two sinus, four urine, five post-abdominal surgery, one oropharyngeal, three pulmonary, one bone, one tonsil, and two post-surgical wound infections
¶Prolonged neutropenia – absolute neutrophil count < 500 cells/mm^3 for greater than ten days prior to receiving voriconazole
¶¶Includes only patients who had neutrophil counts or white blood cell differential counts performed.

Patients less than 12 years of age were entered only in the compassionate use studies. Of the 91 patients treated with voriconazole, 52.8% received voriconazole as primary treatment and 47.3% received voriconazole as salvage therapy (which was considered to be prior systemic antifungal treatment for more than five days). Patients in the compassionate use studies only received salvage therapy.

Duration of therapy

Table A-33 Serious Systemic *Candida* Pooled Efficacy Analysis – Duration of Therapy (Actual Time)

	Systemic *Candida* Infections (N=85)	**Mixed *Candida* Infections* (N=6)**	**Total Serious Systemic *Candida* Infections** (N=91)**
Median duration (days)#	16	8	16
Range (days)	2-342	4-106	2-342

*Patients with *Candida* as part of a mixed infection
**Total number of patients with serious systemic *Candida* infections
#Actual time

Efficacy

Outcome by Primary Underlying Condition

The most common underlying condition was cancer, particularly hematologic malignancies. The success rates in these patients were 18/40 (45.0%) and 15/32 (46.9%), respectively.

Outcome by Hematological Risk Factors and Baseline Neutrophil Count

Among the 22 voriconazole patients with neutropenia at baseline, 12 (60%) had successful outcomes at the End of Therapy. Seven of 17 voriconazole patients with prolonged neutropenia (41.2%), which was considered to be at least 10 days' prior duration, five of 11 voriconazole patients who had any type of bone marrow transplant and three of four patients with relapsed hematologic malignancy had successful outcomes.

Outcome by Site of Infection

Of the 91 patients with *Candida* infections (includes the six patients with mixed fungal infections), 53 had candidemia, and 19 had disseminated infection, with corresponding success rates of 60.4% and 36.8%, respectively. Table A-34 shows successful outcome by site of infection.

Table A-34 Serious Systemic *Candida* Pooled Efficacy Analysis – Outcomes by Site of Infection

Site	Patients with *Candida* (N=85)	Mixed* (N=6)	Total** (N=91)
	Success n/N (%)		
Disseminated#	7/17 (41.2)	0/2	7/19 (36.8)
Blood	31/52 (59.6)	1/1	32/53 (60.4)
Pulmonary	2/2	0/1	2/3
Sinus	1/1	0/1	1/2
Peritoneal fluid	2/5	0	2/5
Oropharyngeal	1/1	0	1/1
Urinary tract/ bladder	4/4	0	4/4
Other##	3/3	1/1	4/4
Total	51/85 (60.0)	2/6	53/91 (58.2)

*Patients with systemic *Candida* as part of a mixed infection
**Total number of patients with serious systemic *Candida* infections
#Disseminated: biopsy-proven skin lesions, hepatosplenic, endophthalmitis, central nervous system, multiple sites excluding esophagus, oropharynx, urine/bladder)
##Includes one bone, one tonsil, two post-surgical wound infections

Clinical Outcome by Species

Successful treatment of infections caused by *Candida* species with voriconazole in serious systemic *Candida* infections (including the six patients with mixed fungal infections that included *Candida* spp.) is shown in Table A-35.

Table A-35 Serious Systemic *Candida* Pooled Efficacy Analysis - *Candida* species Identified and Treated*

Pathogen	Number of Patients with Pathogen	Number of Patients with Successful Outcome	% Success
C. albicans	33	17	51.5
C. glabrata	20	8	40.0
C. tropicalis	13	7	53.8
C. krusei	12	8	66.7
Candida spp.	11	7	63.6
C. parapsilosis	11	10	90.9
Hansenula anomala	1	0	0
Yeast unspecified	1	0	0

*Number of patients with pathogens does not equal the number of patients treated since one patient could have more than one species of *Candida* isolated.

Note that patients with more than one species of *Candida* isolated (e.g., *C. albicans* and *C. krusei*) are included more than once. Thus, the total number of pathogens identified (102) is greater than the total patients (91) with serious systemic *Candida* infections. Voriconazole was effective against a wide range of *Candida* species including the more resistant *C. krusei*. Of the 20 patients treated with voriconazole for *C. glabrata* infection, 12 received voriconazole as salvage therapy, four of whom had successful outcomes. Among the eight patients with primary *C. glabrata* infection, four (50%) had successful outcome. Five of 20 patients with *C. glabrata* infection had severe neutropenia (absolute neutrophil count < 250 cells/mm^3) or graft *vs.* host disease. Of these, two had successful outcomes following treatment with voriconazole. Patients with infection due to *C. krusei*, an organism with intrinsic fluconazole resistance had a 67% successful outcome.

Outcome in Patients Treated with Salvage Therapy

Table A-36 presents success in patients with systemic *Candida* infections who received voriconazole as salvage therapy (> 5 days prior systemic antifungal therapy).

Table A-36 Serious Systemic *Candida* Pooled Efficacy Analysis – Outcome Following Voriconazole as Salvage Therapy by Reason for Salvage Therapy

Reason for Salvage Therapy	Clinical Studies	Compassionate Use	Mixed*	Total**
	Success n/N (%)#			
Prior efficacy failure	10/18 (55.5%)	5/13	1/5	16/36 (44.4)
Intolerance	2/3	1/1	0	3/4
Unknown	2/2	1/1	0	3/3
Total	14/23 (60.9)	7/15 (46.7)	1/5	22/43 (51.2)

*Patients with *Candida* as part of a mixed infection
**All patients with systemic *Candida* infections
#Success = complete or partial response; Failure = stable, failure, unevaluable or discontinued for treatment intolerance or other reasons

The overall success rate in this cohort was higher in the combined clinical studies (60.9%) compared to the compassionate use studies (46.7%). Successful outcomes in salvage therapy patients included 16 of 36 patients (44.4%) classified as efficacy failures. Of these, 26 patients received prior fluconazole, 18 for greater than two weeks, 16 received prior amphotericin B preparations, eight for greater than two weeks, and one received itraconazole for greater than one month.

Pooled Analysis: Esophageal Candidiasis

The objective of the pooled analysis was the consistent assessment of certainty of diagnosis and outcome following voriconazole therapy for esophageal *Candida* infections studies. All patients were assessed and were included in the pooled analysis if they had a definite or probable infection and adequate information for evaluation (detailed methodology for the Voriconazole Efficacy Response Assessment is provided above).

The pooled esophageal candidiasis population included only 32 patients in addition to those treated in the double-blind, randomized Esophageal Candidiasis Study (305), all of whom received voriconazole as salvage rather than primary therapy. The data from these patients will not be discussed in detail. Sixteen of the 32 salvage therapy patients treated with voriconazole had successful outcomes. As expected, the success rate declines in the salvage therapy population compared to the primary population since patients had already failed standard therapy.

Pooled Analysis: Children Aged Two to Less than Twelve Years

Table A- 37 presents the clinical outcome in 34 children aged two to <12 years included in the pooled analysis in the November, 2000 NDA.

Table A- 37 Fungal Infections Pooled Efficacy Analysis - Clinical Outcome and Duration of Therapy in Children (2 to Less than 12 Years)

Fungal infection	Success* N = 15	Stable N = 3	Failure** N = 16	Duration of therapy (range)
Aspergillosis (n = 23)	11 (47.8%)	1 (4.3%)	11 (47.8%)	1-368 days
Systemic *Candida* infection (n = 3)	-	-	3	17-61 days
Scedosporium infections (n = 3)	2 (66.7%)	-	1 (33.3%)	30-419 days
***Other (n = 5)	2 (40.0%)	2 (40.0%)	1 (20.0%)	14-393 days

* Success includes complete and partial response
** Failure includes failure and discontinuation due to intolerance
*** Includes two *Fusarium* spp., one *Alternaria,* one *Trichosporon* and one mixed infection with *A.fumigatus* and *Philaphora richardsiae.*

The efficacy of voriconazole in the therapy of aspergillosis in children was similar to that seen in adults in the compassionate use programs, 47.8% (11/23) and 38.2% (26/68) respectively.

APPENDIX 5. MULTIPLE DOSE VISUAL FUNCTION STUDY (1004): STUDY DESIGN

The Multiple Dose Visual Function Study (1004) was a double blind, randomized, placebo-controlled, parallel group study performed in healthy volunteers to assess the effect of multiple oral doses of voriconazole on the electroretinogram. The study consisted of one study period of 43 days and included 18 subjects in each group. Subjects received oral voriconazole (400mg every 12 hours (q12h) on Day 1 followed by 300mg q12h for 27.5 days) or matched placebo q12h for 28.5 days. Electroretinography (ERG) was performed during screening and on Days 1, 8, 29 and 43. Farnsworth-Munsell 100 Hue, Humphrey visual field, slit lamp, visual acuity, external eye and funduscopy examinations were performed during screening and on Days 3, 7, 28 and 42.

A series of scotopic flashes were administered to assess rod function:

- Step 1: Dim white light (0.001cd-s/m^2)
- Step 2: A standard white stimulus (1.5 to 3cd-s/m^2) was used for maximum response. In order to obtain voltage versus log intensity functions (V logl functions), recordings in response to light flashes in between Steps 1 and 2 were recorded.
- Step 3: The electronic low pass filter was increased to 75 to 100Hz and a standard flash (1.5 to 3cd-s/m^2) was administered with repetitions 15 seconds apart. The subject was subsequently light adapted for 10 minutes to a 17 to 34cd/m^2 background.

A photopic study was then performed:

- Steps 4 and 5: A photopic single flash (1.5 to 3cd-s/m^2) and a 30Hz flicker (1.5 to 3cd-s/m^2) was used in Steps 4 and 5 to assess cone function.

APPENDIX 6. AZOLE EFFECTS ON HEPATIC FUNCTION: A LITERATURE REVIEW

Hepatic function abnormalities tend to be reported at high rates in clinical trials of antifungal agents, regardless of whether an azole or polyene is being studied. The following table summarizes a part of the literature on the frequency of hepatic effects typically seen in clinical trials of antifungal agents, either as treatment of mycoses or as prophylaxis/empirical therapy.

Table A-38 Frequency of Hepatic Effects seen in Clinical Trials of Antifungal Agents in the Literature

Antifungal agent **Hepatic event**	**Comparator antifungal agent** **Hepatic event**	**Type of treatment/population**	**Reference**
Fluconazole: Elevated LFTs – 17/153 (11%)	Placebo control: Elevated LFTs – 19/151 (13%)	Prophylaxis. Neutropenia and cancer	Rotstein *et al.*, 1999
Fluconazole: ALT abnormalities – 29.4%	Placebo control: ALT abnormalities – 21.9%	Prophylaxis. Bone marrow transplant	Goodman *et al.*, 1992
Fluconazole: Elevated bilirubin – 11/36 (31%) Elevated AP – 7/36 (19%) Elevated ALT/AST – 5/36 (14%)	Amphotericin B: Elevated bilirubin – 7/32 (22%) Elevated AP – 2/32 (6%) Elevated ALT/AST – 6/32 (19%)	Prophylaxis. Acute myeloid leukemia	Kern *et al.*, 1998
Fluconazole: Hyperbilirubinemia – 5/52 (10%)	Amphotericin B Hyperbilirubinemia – 9/48 (19%)	Empirical therapy. Febrile neutropenia and cancer	Malik *et al.*, 1998
Fluconazole: Transaminase increase – 10/56 (18%)	Amphotericin B Transaminase increase – 6/56 (11%)	Empirical therapy. Febrile, granulocytopenic cancer patients	Viscoli *et al.*, 1996
Itraconazole: ALT increases – 19/214 (9%)	None	Prophylaxis. Neutropenic patients with hematological malignancy	Bohme *et al.*, 1996
Itraconazole: Increase in aminotransferases – 5/201 (2.5%)	Placebo control: Increase in aminotransferases – 3/204 (1.5%)	Prophylaxis. Neutropenia with hematological malignancy	Menichetti *et al.*, 1999
Itraconazole: Treatment related elevations in transaminases – 10/189 (5%)	None	Chronic therapy of systemic mycoses. Mixed underlying conditions	Tucker *et al.*, 1990
Itraconazole: LFT increases – 7/199 (3.5%)	None	Chronic therapy. Onychomycosis and other fungal infections	De Beule *et al.*, 1991
Itraconazole: Elevated AP – 2/20 (10%) Elevated AST – 8/20 (40%)	Amphotericin B: Elevated AP – 5/20 (25%) Elevated AST – 11/20 (55%)	Treatment of systemic fungal infection. Neutropenia	Van't Wout *et al.*, 1991
Itraconazole: Liver function deterioration – 28/46 (61%)	Placebo: Liver function deterioration – 22/46 (48%)	Prophylaxis. Neutropenic patients with hematological malignancy	Vreugdenhil *et al.*, 1993
L-AMB: Hepatic dysfunction - 23/116 (19.8%)	None	Treatment of fungal infection. Neutropenia	Mills *et al.*, 1994
L-AMB: "Hepatotoxicity" – 11.5%	Amphotericin B: "Hepatotoxicity" – 11.5%	Empirical therapy. Febrile neutropenia	Wingard *et al.*, 2000

Antifungal agent **Hepatic event**	**Comparator antifungal agent** **Hepatic event**	**Type of treatment/population**	**Reference**
<u>L-AMB</u> "Hepatotoxicity" – 61/343 (17.8%) Bilirubinemia – 25/343 (7.3%)	<u>Amphotericin B:</u> "Hepatotoxicity" – 70/344 (20.3%) Bilirubinemia – 29/344 (8.4%)	Empirical therapy. Febrile neutropenia	Walsh *et al.*, 1999

ALT = alanine transaminases; AST = aspartate transaminases; AP = alkaline phosphatase; LFTs = liver function tests

APPENDIX 7. AZOLE EFFECTS ON RENAL FUNCTION: A LITERATURE REVIEW

The following data are seen in comparative trials, principally in subjects with neutropenia and bone marrow transplantation:

Table A-39 Renal Adverse Events in Clinical Studies of Azole Antifungal Agents

Azole antifungal agent Renal event	Comparator antifungal agent Renal event	Type of treatment/population	Reference
Fluconazole: Elevated creatinine – 7/36 (19%)	No treatment control: Elevated creatinine – 1/32 (3%)	Prophylaxis Acute myeloid leukemia	Kern *et al.*, 1998
Fluconazole: Hypokalemia – 12/52 (23%) Nephrotoxicity – 3/52 (6%)	Amphotericin B: Hypokalemia – 25/48 (52%) Nephrotoxicity – 9/48 (19%)	Empiric therapy Cancer patients with neutropenia and prolonged fever	Malik *et al.*, 1998
Fluconazole: Hypokalemia – 1/56 (2%) Nephrotoxicity – 7/56 (13%)	Amphotericin B: Hypokalemia – 20/56 (36%) Nephrotoxicity – 10/56 (18%)	Empirical therapy Granulocytopenic cancer patients with prolonged neutropenia	Viscoli *et al*., 1996
Itraconazole: Abnormal creatinine – 3/20 (15%)	Amphotericin B: Abnormal creatinine – 6/20 (30%)	Treatment of systemic fungal infection Patients with neutropenia	Van't Wout *et al.*, 1991
Itraconazole: Renal function deterioration – 4/46 (9%)	Placebo: Renal function deterioration – 2/46 (4%)	Prophylaxis Neutropenic patients with haematological malignancies	Vreugdenhil *et al*., 1993
Itraconazole: Hypokalemia – 11/189 (6%)	None	Chronic therapy Mixed patients and mixed systemic fungal infections	Tucker *et al*., 1990

APPENDIX 8. PHARMACOKINETIC DATA FROM THERAPEUTIC STUDIES

In 10 therapeutic studies, blood samples for the measurement of plasma voriconazole concentrations were collected from patients at various time points during treatment. More than one blood sample could be collected during a specific dose interval or on different days of treatment. The median number of plasma concentration measurements per patient was 3 (range = 1 - 21). More than 75% of patients had plasma voriconazole concentration measurements. There were 3736 plasma voriconazole concentration measurements from 1053 patients at the time of NDA submission. In these 1053 patients, the median of average and maximum plasma concentrations in individual patients across the studies were 2.51 μg/ml (inter-quartile range = 1.16 – 4.45 μg/ml) and 3.77 μg/ml (inter-quartile range = 2.03 – 6.31 μg/ml), respectively. Average plasma concentrations over the duration of therapy in all of the 1053 patients, were used to investigate the influence of race, age, gender. Subsets of the data from these patients were used to evaluate the influence of weight and baseline hepatic function on pharmacokinetics, as appropriate.

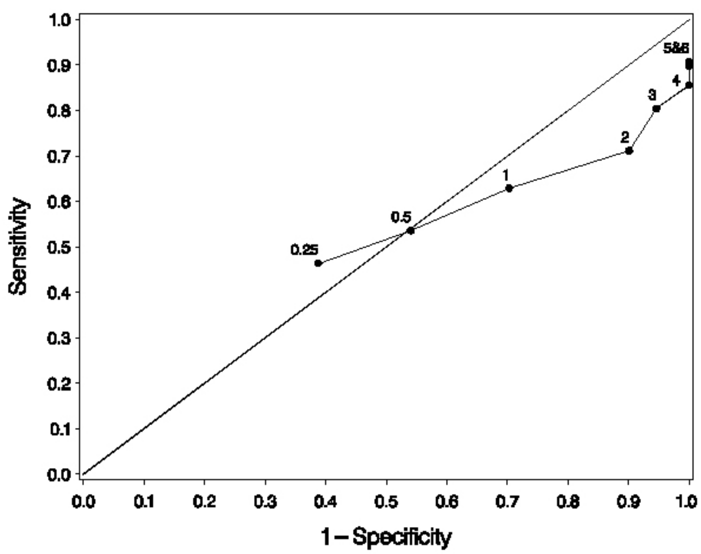
In the Global Comparative Aspergillosis Study (307/602), 618 plasma voriconazole concentration measurements were made in 155 of the 196 voriconazole-treated patients (79%). The median number of samples per patient was 4, with a range of one to 10. In these 155 patients, the median of average and maximum plasma concentrations in individual patients were 2.66 μg/ml (inter-quartile range = 1.60 – 4.18 μg/ml) and 4.44 μg/ml (inter-quartile range = 2.75 – 7.11 μg/ml), respectively. Of the 144 patients included in the Modified Intention to Treat population, 116 (81%) had plasma voriconazole concentration measurements.

APPENDIX 9. ANALYSES OF THE POTENTIAL PREDICTIVE VALUE OF PLASMA VORICONAZOLE CONCENTRATIONS

Receiver Operating Characteristic (ROC) curves were constructed to explore the trade off between the true positive rate (sensitivity) and false positive rate (1-specificity) for every chosen plasma voriconazole concentration cut off. A useful predictive tool should have sensitivity and specificity of at least 0.8, with an ROC curve displayed as a rectangular hyperbola located in the left upper quadrant of the figure. ROC methodology has been applied to cyclosporine monitoring with reported sensitivity and specificity of above 80% for the early prediction of acute graft rejection and nephrotoxicity in renal transplant recipients (Min *et al*, 1998).

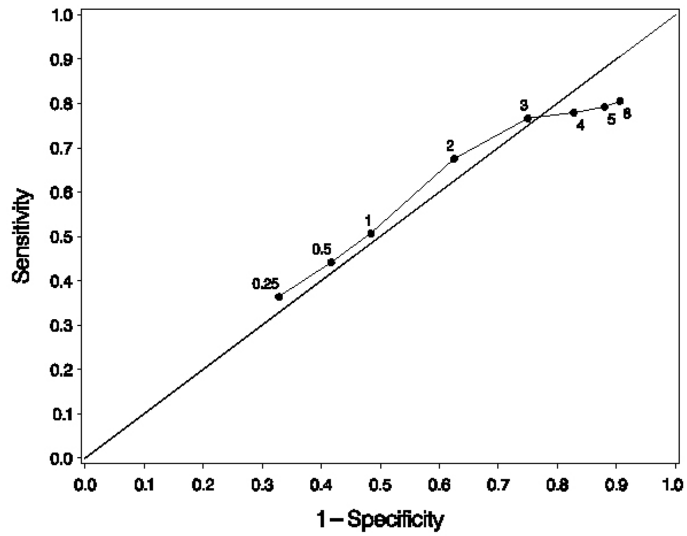
Plasma voriconazole concentrations collected in therapeutic studies in subjects with aspergillosis and candidiasis were included in the analysis. Minimum plasma concentrations below various cut-offs were assessed for the prediction of therapeutic failure. The analyses considered continuous monitoring using all plasma concentration data and only peak (0 – 3 hrs post-dose) or trough (9-12 hrs post-dose) plasma concentrations. Separate analyses were performed for subjects with candidiasis and aspergillosis. For both aspergillosis and candidiasis, the ROC curves (Figure A-1 and Figure A-2, respectively) for prediction of treatment failure from monitoring all plasma voriconazole concentrations lie close to the line of identity i.e. sensitivity = 1-specificity (true positive rate = false positive rate).

Figure A-1 ROC Curve for Predicting Treatment Failure in Aspergillosis from Plasma Voriconazole Concentrations*



*Numbers beside symbols indicate the threshold plasma voriconazole concentration in µg/ml assessed for the prediction of therapeutic failure ; 1134 plasma voriconazole concentrations from 208 patients.

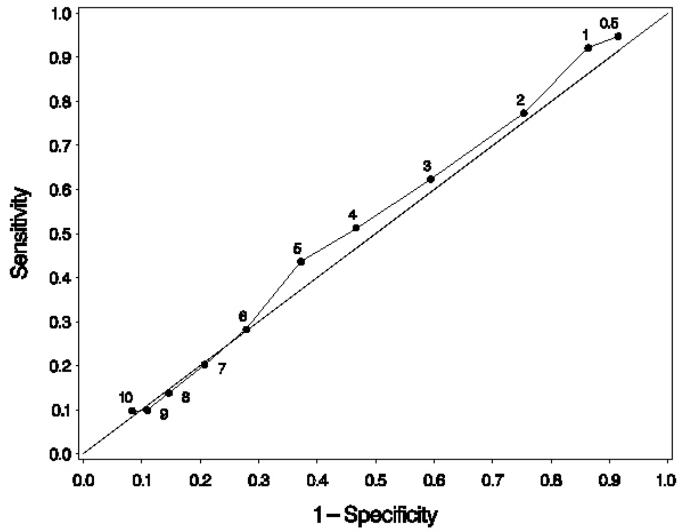
Figure A-2 ROC Curve for Predicting Treatment Failure in Candidiasis from Plasma Voriconazole Concentrations



*Numbers beside symbols indicate the threshold plasma voriconazole concentration in μg/ml assessed for the prediction of therapeutic failure; 762 plasma voriconazole concentrations from 268 patients

For each liver function test, the predictive performance of plasma concentration monitoring for 7 and 14 days and continuously for all the time a patient was in the study (a maximum of 178 days) was investigated. Additionally, continuous monitoring was analyzed using only peak (0 – 3 hrs post-dose) or trough (9-12 hrs post-dose) plasma concentrations. Plasma concentrations above various cut-offs were assessed for the prediction of liver function test abnormality. The ROC curve for ALT abnormalities is presented in Figure A-3 and lies close to the line of identity.

Figure A-3 ROC Curve for Predicting Alanine Transaminase (ALT) Abnormalities from Plasma Voriconazole Concentrations*



*Numbers beside symbols indicate the threshold plasma voriconazole concentration in μg/ml assessed for the prediction of ALT abnormalities; 3736 plasma voriconazole concentrations from 1053 patients

Thus plasma voriconazole concentration was unable to discriminate between true positives and false positives with a similar proportion at various threshold plasma concentrations. No clear optimum upper threshold plasma concentration was identified.

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